FRONT SIDE

150 mm

DATA MATRIX CODE N° 62000000218109

274 mm

Nexium® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not use Nexium 24HR if you are experiencing unexplained weight loss, difficulty swallowing, persistent regurgitation of food or vomiting or vomiting of blood, severe or persistent diarrhoea, blood in the stools or symptoms of gastro-intestinal bleeding, except on medical advice.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant.

Do not take Nexium 24HR if you are pregnant unless your doctor says so.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer
- levothyroxine - a medicine used to treat an underactive thyroid.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet.

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR capsule each day.
Do not take more than the recommended dose.

Swallow Nexium 24HR capsules whole with a glass of water. Do not crush, chew or open the capsules. If the capsules are crushed, chewed or opened, they will not work properly.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium 24HR will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Component Travel Direction

DATA MATRIX CODE N° 62000000218109

V2 13 - Aug - 2025	Artwork Information Panel	HALEON
Non Production Artwork [X]	Production Artwork [ ]	Component No: NPA018400 / AWP No: TR3650440/B
Total Number of Colours including Varnish & Foils: 1		Manufacturing Site: Guayama (Note: North American Artwork will have N/A in this field)
1. Black		Approving Market: Australia
Total Special Finishes: 0		Technical Drawing No: N/A
Studio Location: Asia		Material Spec No: N/A (Note: North American Artwork will have N/A in this field)
		Body Text Size: N/A Smallest Text Size: 3.9pt (Note: For North American Artwork, see Regulatory Spec box for this information)
		Electronic Verification Code: 62000000218109
		Printer and User notes: N/A

AIP_CHAMPS_2023_HALEON

OM-2025-00763-1

REAR SIDE

150 mm

DATA MATRIX CODE N° 62000000218109

274 mm

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Side effects such as dizziness and visual disturbances may uncommonly occur. If affected, you should not drive or use machines.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth
- tiredness.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine
- difficulties urinating.

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body, fainting or difficulties in swallowing
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite
- signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood
- chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath. This could be a sign of a serious condition with your heart.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the bottle until it is time to take them.

If you take **Nexium 24HR** out of the bottle it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the capsules have passed their expiry date, ask your pharmacist what to do with any capsules you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR are approximately 11 x 5mm capsules, with a clear body, and an amethyst cap imprinted with "NEXIUM 20MG" in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

Ingredients
Each **Nexium 24HR** capsule contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20 mg.

Plus the following inactive ingredients,

Capsule content

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Polysorbate 80
- Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
- Purified talc
- Triethyl citrate
- Titanium dioxide (E171)
- Carmine (E120)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

Capsule shell

- Gelatin
- Erythrosine
- Indigo carmine (E132)
- Allura red AC (E129)

Printing ink

- Povidone
- Propylene glycol
- Shellac
- Sodium hydroxide
- Titanium dioxide (E171)

Band

- Gelatin
- Iron oxide yellow (E172)

Nexium 24HR capsules are available in a bottle of 14 capsules
The bottle contains a sealed container with silica gel dessicant.

Sponsor

Haleon
Sydney, NSW, Australia

AU: 1800 028 533

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 316501
This leaflet was prepared June 2025.

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NPA018400

Component Travel Direction

DATA MATRIX CODE N° 62000000218109

V2 13 - Aug - 2025	Artwork Information Panel	HALEON

Non Production Artwork	X	Production Artwork		Component No: NPA018400	AWP No: TR3650440/B

Total Number of Colours including Varnish & Foils: 1

1. Black					

Total Special Finishes: 0

Studio Location: Asia

Manufacturing Site: Guayama (Note: North American Artwork will have N/A in this field)
Approving Market: Australia
Technical Drawing No: N/A
Material Spec No: N/A (Note: North American Artwork will have N/A in this field)
Body Text Size: N/A
Smallest Text Size: 3.9pt (Note: For North American Artwork, see Regulatory Spec box for this information)
Electronic Verification Code: 62000000218109
Printer and User notes: N/A

AIP_CHAMPS_2023_HALEON

OM-2025-00763-1

FRONT SIDE

Attachment 2

DATA MATRIX CODE N° XXXXXXXXX

274 mm

Nexium® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not use Nexium 24HR if you are experiencing unexplained weight loss, difficulty swallowing, persistent regurgitation of food or vomiting or vomiting of blood, severe or persistent diarrhoea, blood in the stools or symptoms of gastro-intestinal bleeding, except on medical advice.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant.

Do not take Nexium 24HR if you are pregnant unless your doctor says so.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet.

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR capsule each day.
Do not take more than the recommended dose.

Swallow Nexium 24HR capsules whole with a glass of water. Do not crush, chew or open the capsules. If the capsules are crushed, chewed or opened, they will not work properly.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium 24HR will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Component Travel Direction

DATA MATRIX CODE N° XXXXXXXXX

V2 01 - AUG - 2024	Artwork Information Panel	HALEON

Non Production Artwork [X]	Production Artwork [ ]	Component No: NPA016245	AWP No: 7764757

Total Number of Colours including Varnish & Foils: 1

70% 50% 20%					
1. Black	2.	3.	4.	5.	6.
7.	8.	9.	10.	11.	12.

Total Special Finishes: 0

Manufacturing Site:
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: AWDRG-443 v1

Material Spec No:
(Note: North American Artwork will have N/A in this field)

Body Text Size: 6.75pt
Smallest Text Size: 6.7pt
(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

AIP_CHAMPS_2023_HALEON

REAR SIDE

150 mm

DATA MATRIX CODE N° XXXXXXXXX

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Side effects such as dizziness and visual disturbances may uncommonly occur. If affected, you should not drive or use machines.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth
- tiredness.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine
- difficulties urinating.

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body, fainting or difficulties in swallowing
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite
- signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood
- chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath. This could be a sign of a serious condition with your heart.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the bottle until it is time to take them.

If you take **Nexium 24HR** out of the bottle it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the capsules have passed their expiry date, ask your pharmacist what to do with any capsules you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR are approximately 11 x 5mm capsules, with a clear body, and an amethyst cap imprinted with "NEXIUM 20MG" in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

Ingredients
Each **Nexium 24HR** capsule contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20 mg.

Plus the following inactive ingredients,

Capsule content

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Polysorbate 80
- Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
- Purified talc
- Triethyl citrate
- Titanium dioxide (E171)
- Carmine (E120)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

Capsule shell

- Gelatin
- Erythrosine
- Indigo carmine (E132)
- Allura red AC (E129)

Printing ink

- Povidone
- Propylene glycol
- Shellac
- Sodium hydroxide
- Titanium dioxide (E171)

Band

- Gelatin
- Iron oxide yellow (E172)

Nexium 24HR capsules are available in a bottle of 14 capsules
The bottle contains a sealed container with silica gel dessicant.

Sponsor

Haleon
Sydney, NSW, Australia

AU: 1800 028 533

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 316501
This leaflet was prepared July 2024.

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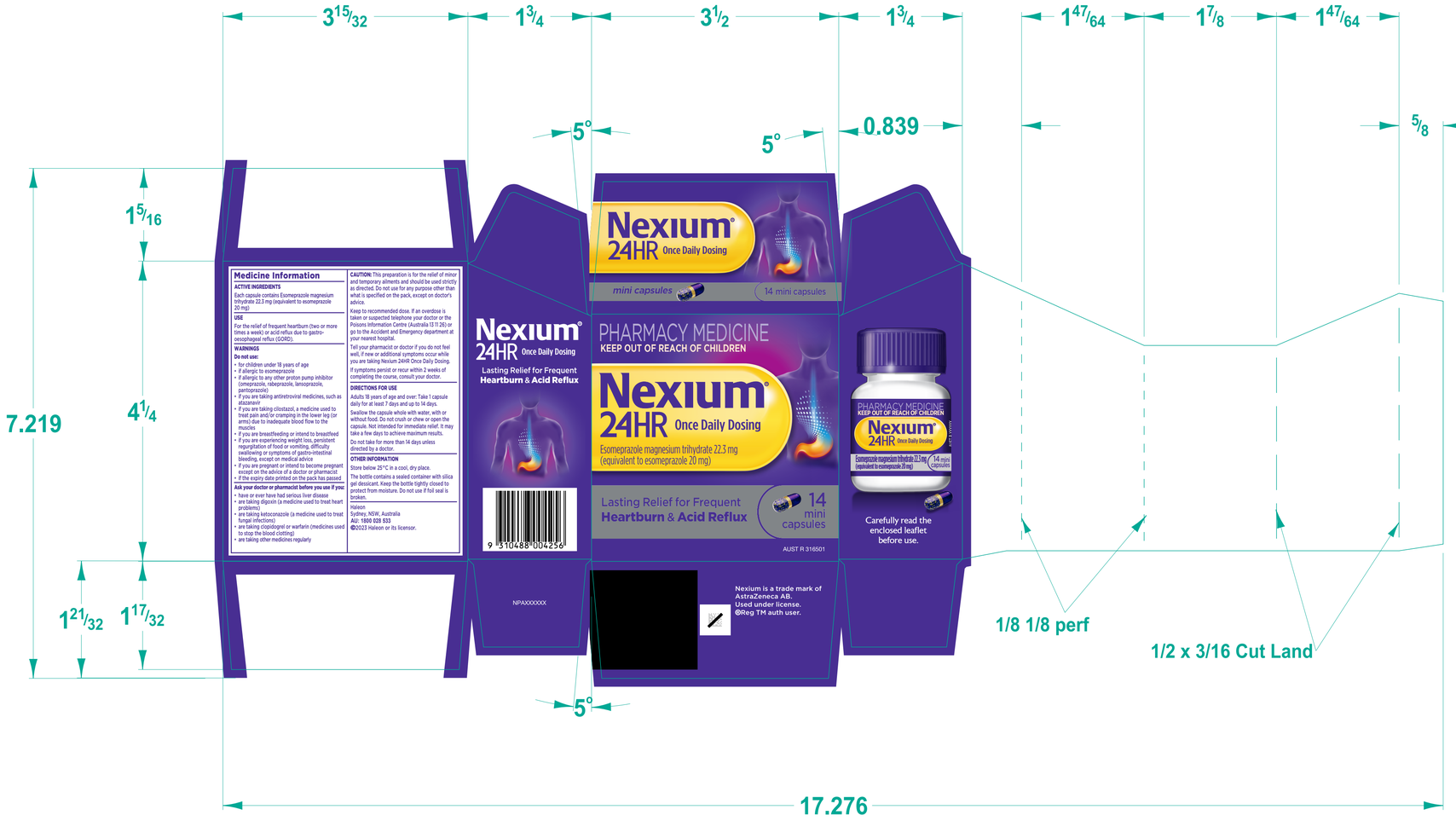
Component Travel Direction

DATA MATRIX CODE N° XXXXXXXXX

V2 01 - AUG - 2024	Artwork Information Panel					HALEON
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70% 50% 20%						Approving Market: Australia-AUS
1. Black	2.	3.	4.	5.	6.	Technical Drawing No: AWDRG-443 v1
						Material Spec No: (Note: North American Artwork will have N/A in this field)
7.	8.	9.	10.	11.	12.	Body Text Size: 6.75pt / Smallest Text Size: 6.7pt (Note: For North American Artwork, see Regulatory Spec box for this information)
Total Special Finishes: 0						Electronic Verification Code:
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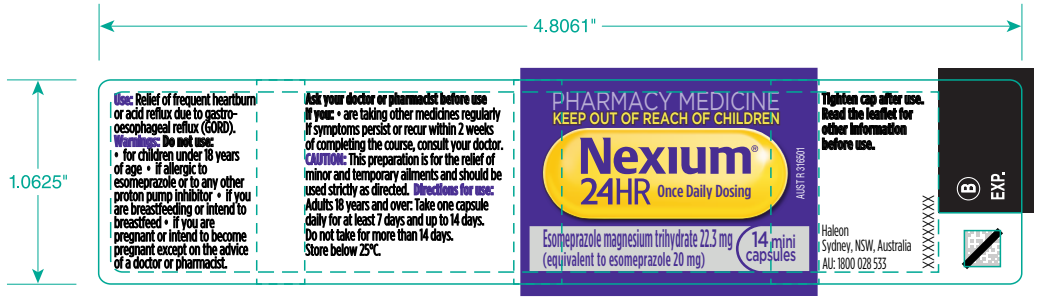
AIP_CHAMPS_2023_HALEON

OM-2024-00977-1



V2 11 - DEC - 2023	Artwork Information Panel	HALEON
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Total Number of Colours including Varnish & Foils: 8		Manufacturing Site:
1. Cyan	2. Yellow	3. Black	4. White 1	5. PANTONE 2607 C	6. PANTONE Rhodamine Red C	Approving Market: Australia-AUS
Hot Foil 7. (SILVER)	8. Varnish - GLOSS	9.	10.	11.	12.	Technical Drawing No: 8951_C
Total Special Finishes: 1						Material Spec No:
Emboss						Body Text Size: 6.25pt Smallest Text Size: 6.0pt
						Electronic Verification Code:
						Printer and User notes:

AIP_CHAMPS_2023_HALEON



V2
01 - DEC - 2023

Artwork Information Panel

HALEON

Non Production Artwork	X	Production Artwork	

Total Number of Colours including Varnish & Foils: 6

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Total Special Finishes: 0

Component No:	AWP No:
NPA013773	7526550

Manufacturing Site:
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: AWDRG-442

Material Spec No:
(Note: North American Artwork will have N/A in this field)

Body Text Size: 6.0pt
Smallest Text Size: 4.0pt
(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

AIP_CHAMPS_2023_HALEON

FRONT SIDE

DATA MATRIX CODE N° XXXXXX

274 mm

Nexium® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant unless your doctor says so.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet.

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR capsule each day.

Swallow Nexium 24HR capsules whole with a glass of water. Do not crush, chew or open the capsules. If the capsules are crushed, chewed or opened, they will not work properly.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium 24HR will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Component Travel Direction

DATA MATRIX CODE N° XXXXXX

V2 23 - DEC - 2023	Artwork Information Panel	HALEON

Non Production Artwork [X]	Production Artwork [ ]	Component No: NPA014063	AWP No: 7547062

Total Number of Colours including Varnish & Foils: 1

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7.	8.	9.	10.	11.	12.

Total Special Finishes: 0

Manufacturing Site: NA
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: AWDRG-443

Material Spec No: NA
(Note: North American Artwork will have N/A in this field)

Body Text Size: 6.75pt
Smallest Text Size: 6.7pt
(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

AIP_CHAMPS_2023_HALEON

REAR SIDE

150 mm

DATA MATRIX CODE N° XXXXXX

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- “pins and needles”
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.
- Signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the bottle until it is time to take them.

If you take **Nexium 24HR** out of the bottle it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the capsules have passed their expiry date, ask your pharmacist what to do with any capsules you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR are approximately 11 x 5mm capsules, with a clear body, and an amethyst cap imprinted with “NEXIUM 20MG” in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

Ingredients
Each **Nexium 24HR** capsule contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20 mg.

Plus the following inactive ingredients,

Capsule content
- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Polysorbate 80
- Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
- Purified talc
- Triethyl citrate
- Titanium dioxide (E171)
- Carmine (E120)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

Capsule shell
- Gelatin
- Erythrosine
- Indigo carmine (E132)
- Allura red AC (E129)

Printing ink
- Povidone
- Propylene glycol
- Shellac
- Sodium hydroxide
- Titanium dioxide (E171)

Band
- Gelatin
- Iron oxide yellow (E172)

Nexium 24HR capsules are available in a bottle of 14 capsules
The bottle contains a sealed container with silica gel dessicant.

Sponsor

Haleon
Sydney, NSW, Australia

AU: 1800 028 533

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 316501
This leaflet was prepared January 2024.

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NPA014063

Component Travel Direction

DATA MATRIX CODE N° XXXXXX

V2 23 - DEC - 2023	Artwork Information Panel	HALEON

Non Production Artwork [X]	Production Artwork [ ]	Component No: NPA014063	AWP No: 7547062

Total Number of Colours including Varnish & Foils: 1

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7.	8.	9.	10.	11.	12.

Total Special Finishes: 0

Manufacturing Site: NA
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: AWDRG-443

Material Spec No: NA
(Note: North American Artwork will have N/A in this field)

Body Text Size: 6.75pt
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(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

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AUSTRALIAN PRODUCT INFORMATION

NEXIUM® 24HR Once Daily Dosing
(Esomeprazole magnesium trihydrate)

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule or tablet of NEXIUM 24HR Once Daily Dosing (referred as NEXIUM 24HR elsewhere in this Product Information) contains esomeprazole magnesium trihydrate 22.3 mg (equivalent to esomeprazole 20 mg) as enteric-coated pellets.

Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

Excipient(s) with known effect:
Sucrose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 24HR 20 mg capsules are approximately 11 x 5 mm with a clear body, and an amethyst cap imprinted with “NEXIUM 20 MG” in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

NEXIUM 24HR 20 mg tablets are light pink, oblong, biconvex, film-coated tablet engraved “20 mg” on one side and “A/EH” on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

NEXIUM 24HR is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults
For symptomatic treatment of gastro-oesophageal reflux disease (GORD), take 1 capsule (20 mg) or tablet (20 mg) once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persist or worsen while taking this course, or if symptoms persist or recur within two weeks of completing the course.

Children below the age of 18 years:
NEXIUM 24HR is not intended for use in children under the age of 18.

Method of administration
NEXIUM 24HR capsules or tablets should be swallowed whole with liquid. The capsules or tablets must not be chewed, crushed or opened.

If required, the NEXIUM 24HR tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Dosage adjustment

Geriatrics
Dose adjustment is not required in the elderly.

Hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM 24HR should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment
Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3. CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Effects of esomeprazole on other drugs).

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases

gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

CYP2C19 enzyme
Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Hypomagnesaemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Gender
Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM 24HR.

Use in hepatic impairment
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for

the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Paediatric use
NEXIUM 24HR is not intended for use in children under the age of 18.

Use in the elderly
The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Effect on laboratory tests
Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5 to 14 days before CgA measurement and that measurements should be repeated if levels have not normalised by this time.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Other drugs that affect esomeprazole

Clarithromycin
Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride
In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, Clomipramine and Imipramine
Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam
Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs
Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any

clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin
Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate
When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs
Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs is not recommended.

Medicinal products with pH dependent absorption
The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to

30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxycillin or quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy - Category B3
For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM 24HR should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation
It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM 24HR should not be used during breast feeding.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM 24HR is well tolerated.

Clinical trials and post-marketing data
The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders
Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders
Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders
Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders
Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances
Rare: blurred vision

Ear and labyrinth disorders
Uncommon: vertigo

Respiratory, thoracic mediastinal disorders
Rare: bronchospasm

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis
Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Hepatobiliary disorders
Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders
Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders
Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: gynaecomastia

General disorders and administration site conditions
Rare: malaise, hyperhidrosis

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful.

Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised. No specific antidote is known.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
NEXIUM 24HR (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H+, K+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+, K+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	**% time intragastric pH > 4**	**p-value**
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001

	n	% time intragastric pH > 4	p-value
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition
During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Symptomatic treatment of GORD in patients with normal endoscopy
At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or H. pylori status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

5.2. PHARMACOKINETIC PROPERTIES

Absorption
Esomeprazole is acid labile and is administered orally as enteric coated pellets in capsules or tablets. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo*

conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20 mg esomeprazole and increases to 68% after repeated once daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism
Esomeprazole is completely metabolised by the cytochrome P-450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion
The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM 24HR is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity
Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H2-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

NEXIUM 24HR capsules:

Capsule content
Glyceryl monostearate
Hyprolose
Hypromellose
Magnesium stearate
Methacrylic acid copolymer
Polysorbate 80
Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
Purified Talc
Triethyl citrate
Titanium dioxide (E171)
Carmine (E120)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

Capsule shell
Gelatin
Erythrosine
Indigo carmine (E132)
Allura red AC (E129)

Printing ink
Povidone
Propylene glycol
Shellac
Sodium hydroxide
Titanium dioxide (E171)

Band
Gelatin
Iron oxide yellow (E172)

NEXIUM 24HR tablets:
Glyceryl monostearate
Hyprolose
Hypromellose
Magnesium stearate
Methacrylic acid copolymer
Microcrystalline cellulose
Synthetic paraffin
Macrogol 6000
Polysorbate 80
Crospovidone
Sodium stearylfumarate
Purified talc
Triethyl citrate
Sugar spheres (maize starch and sucrose)
Titanium dioxide
Iron oxide red CI77491
Iron oxide yellow CI77492

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Store in the original package in order to protect from moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

NEXIUM 24HR capsules:

Container type
High-density polyethylene (HDPE) bottle with an induction seal closure and child resistant closure containing 14 capsules. The bottle also contains a sealed container with silica gel desiccant.

Pack size
NEXIUM 24HR capsules are available in a bottle of 14 capsules.

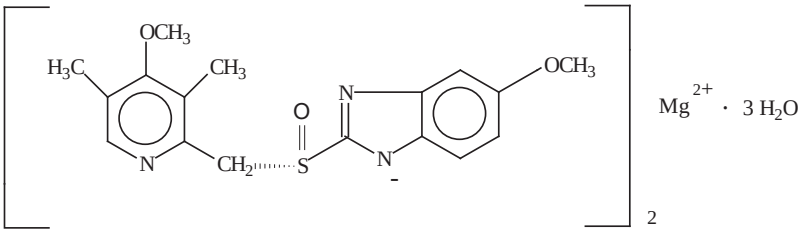
NEXIUM 24HR tablets:
NEXIUM 24HR tablets are available in blister pack of 7 and 14 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure
The chemical name of esomeprazole magnesium trihydrate is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate.



Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$
Molecular weight: 767.2 (trihydrate)

CAS number
217087-09-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 2 – Pharmacy Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

8. SPONSOR

GlaxoSmithKline Consumer Healthcare Australia Pty Ltd trading as Haleon

Level 48, 8 Parramatta Square,

10 Darcy Street, Parramatta NSW 2150

9. DATE OF FIRST APPROVAL

NEXIUM 24HR capsules: 15 April 2019
NEXIUM 24HR tablets: 04 December 2014

10. DATE OF REVISION

19 September 2022

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Summary table of changes

Sections changed	Summary of new information
4.4	Addition of hypomagnesaemia
8	Update to sponsor name and address

NEXIUM® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking Nexium 24HR against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux. This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week. **Nexium 24HR** is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under the age of 18.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or

vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition

- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant unless your doctor says so. Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

- atazanavir - medicine used to treat viral infections such as HIV
- cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include**:**

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR capsule each day.

Swallow Nexium 24HR capsules whole with a glass of water. Do not crush, chew or open the capsules. If the capsules are chewed or crushed they will not work properly.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking NEXIUM 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist or that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.
- Signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood.

These are very serious side effects. You may need urgent medical treatment or hospitalisation. Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the bottle until it is time to take them.

If you take **Nexium 24HR** out of the bottle it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the capsules have passed their expiry date, ask your pharmacist what to do with any capsules you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR are approximately 11 x 5 mm capsules with a clear body, and an amethyst cap imprinted with "NEXIUM 20MG" in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

Ingredients

Each **Nexium 24HR** capsule contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients,

Capsule content

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Polysorbate 80
- Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
- Purified Talc
- Triethyl citrate
- Titanium dioxide (E171)
- Carmine (E120)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

Capsule shell

- Gelatin
- Erythrosine
- Indigo carmine (E132)
- Allura red AC (E129)

Printing ink

- Povidone
- Propylene glycol
- Shellac
- Sodium hydroxide
- Titanium dioxide (E171)

Band

- Gelatin
- Iron oxide yellow (E172)

Nexium 24HR capsules are available in a bottle of 14 capsules.

The bottle contains a sealed container with silica gel desiccant.

Sponsor

GlaxoSmithKline Consumer Healthcare trading as Haleon,

Sydney, NSW, Australia

AU: 1800 028 533

This leaflet was prepared October 2022.

Australian Registration Number

Nexium 24HR Once Daily Dosing:

AUST R 316501

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AUSTRALIAN PRODUCT INFORMATION

NEXIUM® 24HR Once Daily Dosing Hard Capsules
(Esomeprazole magnesium trihydrate)

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of Nexium 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this Product Information) contains esomeprazole magnesium trihydrate 22.3 mg (equivalent to esomeprazole 20 mg) as enteric-coated pellets.

Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

Excipients with known effect:
Sucrose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Nexium 24HR 20 mg hard capsules are approximately 11 x 5 mm with a clear body, and an amethyst cap imprinted with NEXIUM 20 MG" in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

NEXIUM 24HR is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults
For symptomatic treatment of gastro-oesophageal reflux disease (GORD), take 1 capsule (20 mg) once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persist or worsen while taking this course, or if symptoms persist or recur within two weeks of completing the course.

Children below the age of 18 years:
NEXIUM 24HR is not intended for use in children under the age of 18.

Method of administration
NEXIUM 24HR hard capsules should be swallowed whole with liquid. The capsules must not be chewed, crushed or opened.

Dosage adjustment

Geriatrics
Dose adjustment is not required in the elderly.

Hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM 24HR should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment
Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3. CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Effects of esomeprazole on other drugs).

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as Salmonella and Campylobacter and, in hospitalised patients, possibly also Clostridium difficile.

CYP2C19 enzyme
Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is

most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Gender
Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM 24HR.

Use in hepatic impairment
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Paediatric use
NEXIUM 24HR is not intended for use in children under the age of 18.

Use in the elderly
The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Effect on laboratory tests
Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5 to 14 days before CgA measurement and that measurements should be repeated if levels have not normalised by this time.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics

of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Other drugs that affect esomeprazole

Clarithromycin
Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride
In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life (t½) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased Cmax and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, Clomipramine and Imipramine
Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel+the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam
Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs
Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin
Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs
Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs is not recommended.

Medicinal products with pH dependent absorption
The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxycillin or quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy - Category B3
For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM 24HR should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of

about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation
It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM 24HR should not be used during breast feeding

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Nexium 24HR is well tolerated.

Clinical trials and post-marketing data
The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders
Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders
Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders
Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders
Common: headache
Uncommon: dizziness, paraesthesia, somnolence

Rare: taste disturbance

Eye disturbances
Rare: blurred vision
Ear and labyrinth disorders
Uncommon: vertigo

Respiratory, thoracic mediastinal disorders
Rare: bronchospasm

Gastrointestinal
Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis

Hepatobiliary disorders
Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders
Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders
Rare: arthralgia, myalgia
Very rare: muscular weakness
Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: gynaecomastia

General disorders and administration site conditions
Rare: malaise, hyperhidrosis

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful.

Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised. No specific antidote is known.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
Nexium 24HR (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H+, K+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+, K+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion
After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition
During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Symptomatic treatment of GORD in patients with normal endoscopy
At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or H. pylori status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

5.2. PHARMACOKINETIC PROPERTIES

Absorption
Esomeprazole is acid labile and is administered orally as enteric coated pellets in capsules. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. In vivo conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20mg esomeprazole and increases to 68% after repeated once daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism
Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after

repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion
The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM 24HR is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an in vitro chromosome aberration test in human lymphocytes. However, two in vivo tests (a mouse micronucleus test and an in vivo chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under in vivo conditions. Exposure levels in man are well below those at which clastogenic effects occurred in vitro.

Carcinogenicity
Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H2-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Capsule content
Glyceryl monostearate
Hyprolose

Hypromellose
Magnesium stearate
Methacrylic acid copolymer
Polysorbate 80
Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
Purified Talc
Triethyl citrate
Titanium dioxide (E171)
Carmine (E120)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

Capsule shell
Gelatin
Erythrosine
Indigo carmine (E132)
Allura red AC (E129)

Printing ink
Povidone
Propylene glycol
Shellac
Sodium hydroxide
Titanium dioxide (E171)

Band
Gelatin
Iron oxide yellow (E172)

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

NEXIUM 24HR hard capsules should be stored below 25°C.

Store in the original package in order to protect from moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

Container type
High-density polyethylene (HDPE) bottle with an induction seal closure and child

resistant closure containing 14 capsules. The bottle also contains a sealed container with silica gel desiccant.

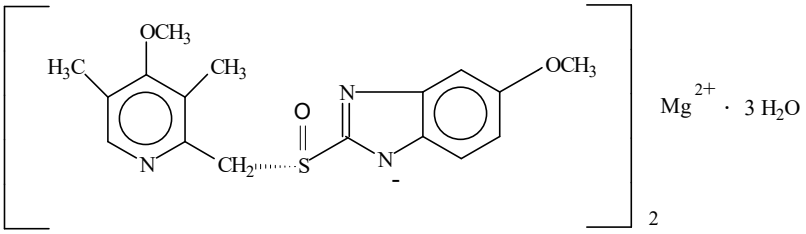
Pack size
Nexium 24HR hard capsules are available in a bottle of 14 capsules.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure
The chemical name of esomeprazole magnesium trihydrate is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate.



Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$
Molecular weight: 767.2 (trihydrate)

CAS number
217087-09-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 2 – Pharmacy Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

8. SPONSOR

Pfizer Australia Pty Limited
Level 15-18, 151 Clarence Street
Sydney NSW 2000

9. DATE OF FIRST APPROVAL

DD Month YYYY

10. DATE OF REVISION

DD Month YYYY

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NEXIUM® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium 24HR** Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet). It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking Nexium 24HR against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux. This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week. **Nexium 24HR** is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under the age of 18.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or

vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition

- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant unless your doctor says so. Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take Nexium 24HR while you are pregnant. It may affect your baby.

Do not take Nexium24HR if you are breasfeeding.Ask your doctor for more information.

It is not known if Nexium 24HR is excreted in breast milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

- atazanavir - medicine used to treat viral infections such as HIV
- cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Nexium 24HR. These include**:**

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR capsule each day.

Swallow Nexium 24HR capsules whole with a glass of water. Do not crush , chew or open the capsules. If the capsules are chewed or crushed they will not work properly.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking NEXIUM 24HR

Things you must do

If you are about to be started on any new medicine, tell your doctor, dentist or pharmacist that you are taking Nexium 24HR.

Tell all doctors, dentists and pharmacists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

These are very serious side effects. You may need urgent medical treatment or hospitalisation. Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the bottle until it is time to take them.

If you take **Nexium 24HR** out of the bottle it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the capsules have passed their expiry date, ask your pharmacist what to do with any capsules you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR are approximately 11 x 5 mm capsules with a clear body, and an amethyst cap imprinted with "NEXIUM 20 MG" in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

Ingredients

Each **Nexium 24HR** capsule contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients,

Capsule content

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Polysorbate 80
- Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
- Purified Talc
- Triethyl citrate
- Titanium dioxide (E171)
- Carmine (E120)
- Indigo carmine aluminium lake (E132)
- Iron oxide yellow (E172)

Capsule shell

- Gelatin
- Erythrosine
- Indigo carmine (E132)
- Allura red AC (E129)

Printing ink

- Povidone
- Propylene glycol
- Shellac
- Sodium hydroxide
- Titanium dioxide (E171)

Band

- Gelatin
- Iron oxide yellow (E172)

Nexium 24HR capsules are available in bottles of 14 capsules.

The bottle contains a sealed container with silica gel desiccant.

Sponsor

Pfizer Australia Pty Limited

Sydney Australia

This leaflet was prepared April 2018.

Australian Registration Number

Nexium 24HR Once Daily Dosing:

AUST R

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SIZE - 4.8061" x 1.0625"
(CR: 0.0625")

No Print Area

Printable area FPO - bottle round corners

Data Matrix Location

Job Name:	78127 Nexium Australia 14s MINI CAPSULE LABEL		
Client:	PFIZER		
DBG Job No.:	78127	Date:	07.12.2018
Item Code:	WL 1301	Package Code:	NA
Proof No.:	8		
Dimensions:	4.8061" wide x 1.0625" deep | 0.0625" corner radius		

Colours: YK, PANTONE 2607 C, PANTONE Rhodamine Red, SILVER METALLIC

PLEASE EXAMINE THIS PROOF CAREFULLY

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DBG creative agency
4/106 Grose street, Parramatta NSW 2150
PO Box 3126 North Parramatta NSW 1750
Ph: 02 9630 1733 Fax: 02 9630 1930
info@dbgraphics.com.au
www.dbgraphics.com.au



SIZE - 4.8061" x 1.0625"
(CR: 0.0625")

No Print Area

Printable area FPO - bottle round corners

Data Matrix Location

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Medicine Information

Active Ingredient:

Each capsule contains Esomeprazole magnesium trihydrate 22.3 mg (equivalent to esomeprazole 20 mg)

Use:

For the relief of frequent heartburn (two or more times a week) or acid reflux due to gastro-oesophageal reflux (GORD).

Warnings:

Do not use:

- for children under 18 years of age
- if allergic to esomeprazole
- if allergic to any other proton pump inhibitor (omeprazole, rabeprazole, lansoprazole, pantoprazole)
- if you are taking antiretroviral medicines, such as atazanavir
- if you are taking cilostazol, a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles
- if you are breastfeeding or intend to breastfeed
- if the expiry date printed on the pack has passed

Ask your doctor or pharmacist before use if you:

- are pregnant or intend to become pregnant
- have or ever have had serious liver disease
- are taking digoxin (a medicine used to treat heart problems)
- are taking ketoconazole (a medicine used to treat fungal infections)
- are taking clopidogrel or warfarin (medicines used to stop the blood clotting)
- are taking other medicines regularly

CAUTION: This preparation is for the relief of minor and temporary ailments and should be used strictly as directed.

Keep to recommended dose. If an overdose is taken or suspected telephone your doctor or the Poisons Information Centre (Australia 13 11 26) or go to the Accident and Emergency department at your nearest hospital.

Tell your pharmacist or doctor if you do not feel well while you are taking Nexium 24HR Once Daily Dosing.

If symptoms persist or recur within 2 weeks of completing the course, consult your doctor.

Directions for use:

Adults 18 years of age and over: Take 1 capsule daily for at least 7 days and up to 14 days.

Swallow the capsule whole with water, with or without food. Do not crush, chew or open the capsule. Not intended for immediate relief. It may take a few days to achieve maximum results.

Do not take for more than 14 days unless directed by a doctor.

Other Information:

Store below 25°C in a cool, dry place.

The bottle contains a sealed container with silica gel dessicant. Keep the bottle tightly closed to protect from moisture. Do not use if foil seal is broken.

Marketed by

PFIZER AUSTRALIA PTY LIMITED,
SYDNEY, AUSTRALIA
Toll Free 1800 555 057

© Pfizer 2018

Nexium®
Once Daily Dosing (24HR

Lasting Relief for Frequent
Heartburn & Acid Reflux



9310488002375

WC1552

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Nexium®
Once Daily Dosing (24HR

Esomeprazole magnesium trihydrate 22.3 mg
(equivalent to esomeprazole 20 mg)

Lasting Relief for Frequent
Heartburn & Acid Reflux

14 mini capsules

AUST R XXXXXX

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Carefully read the enclosed leaflet before use.

Job Name:	78127 Nexium Australia 14s MINI CAPSULE CARTON
Client:	PFIZER
DBG Job No.:	78127 Date: 07.12.2018
Item Code:	WC1552 Package Code: NA
Proof No.:	4
Dimensions:	439.122mm wide x 206.642mm deep (FLAT CARTON)

Colours: CYK; PANTONE 2607 C; PANTONE Rhodamine Red; Silver Foil; Gloss Varnish; Embossing; Embossing 2nd Level

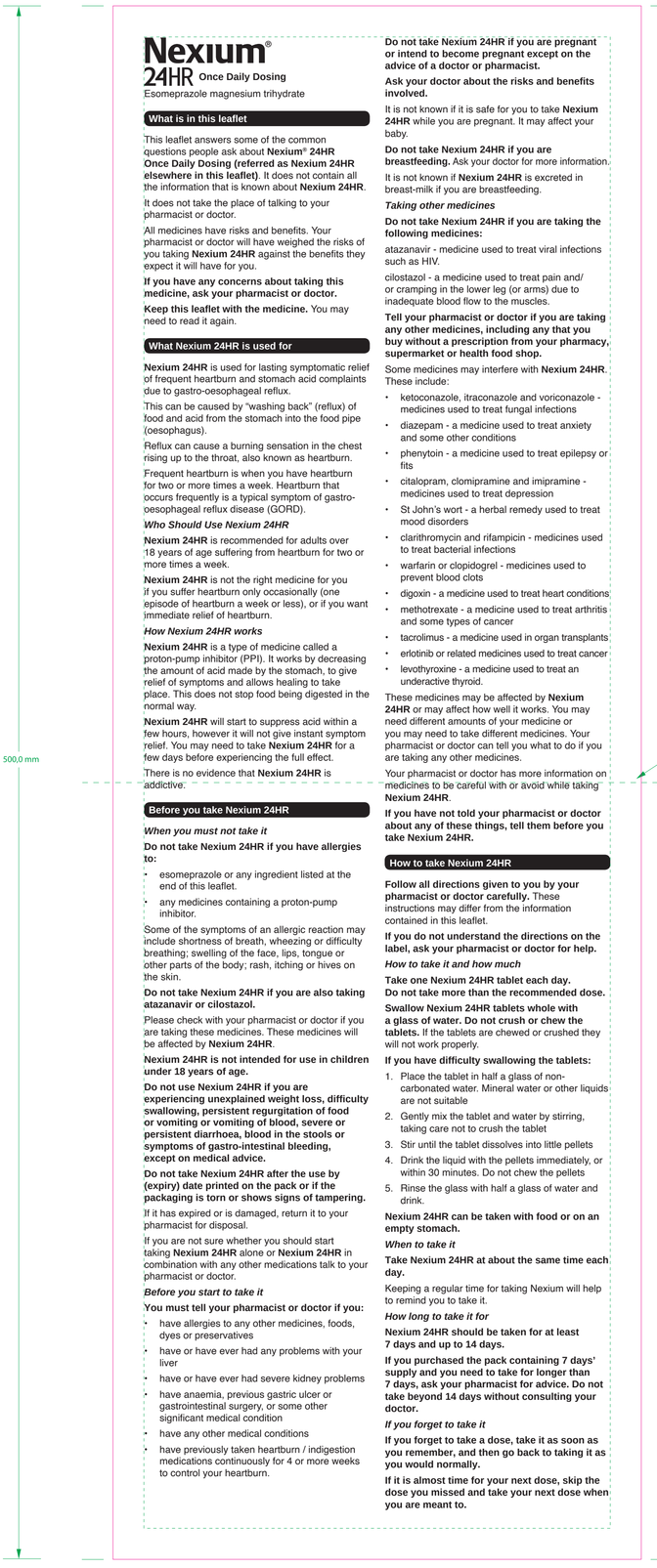
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Front side



Nexium® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not use Nexium 24HR if you are experiencing unexplained weight loss, difficulty swallowing, persistent regurgitation of food or vomiting or vomiting of blood, severe or persistent diarrhoea, blood in the stools or symptoms of gastro-intestinal bleeding, except on medical advice.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn.

Do not take Nexium 24HR if you are pregnant or intend to become pregnant except on the advice of a doctor or pharmacist.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV.

cilostazol - a medicine used to treat pain and/ or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer
- levothyroxine - a medicine used to treat an underactive thyroid.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

Pre-folding

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet.

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.
Do not take more than the recommended dose.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor.

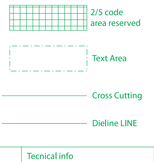
If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Scale 1:1





Ver.	Date	Reason for revision	Author	Note	Tecnical info
01	19 May 2011	New Drawing	A. Gaudio	Used for:	Scale: 1:1
02	10 Jan 2018	Eliminate read direction pharmacode	B. Bornago		Two side leaflet (front/back) dim. unfolded leaflet: 170 x 500 mm dim. folded leaflet: Refer to Material Spec
03	27 July 2023	Update info table	B. Bornago		

Artwork&Packaging APRILIA DEPT

Description: **Leaflet**

Drawing no.: **WYA0215**

APRILIA

Site Additional Artwork Information Panel

Varnish type: XXXXX

Reel unwind: XXXXX

V3 27 - Aug - 2025

Artwork Information Panel **HALEON**

Non Production Artwork [X] Production Artwork [ ]

Total Number of Colours including Varnish & Foils: 1

Black 1.

Total Special Finishes: 0

Studio Location: Asia

Component No: NPA018379	AWP No: TR3623983/C
Manufacturing Site: Aprilia (Italy - Nexium - Multipack - 14 pack and 7 pack, from 1 to 3 tabs pack)	
Approving Market: Australia / New Zealand	
Technical Drawing No: WYA0215 v03	
Material Spec No: N/A (Italy - Nexium - Multipack - 14 pack and 7 pack, from 1 to 3 tabs pack)	
Body Text Size: N/A	Smallest Text Size: 8.0pt (Italy - Nexium - Multipack - 14 pack and 7 pack, from 1 to 3 tabs pack)
Electronic Verification Code: N/A	
Printer and User notes: N/A	

AWP_DRAWER_2020_HALEON

OM-2025-00826-1



Rear side

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (Australia 13 11 26, or New Zealand 0800 764 766) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Side effects such as dizziness and visual disturbances may uncommonly occur. If affected, you should not drive or use machines.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth
- tiredness.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine
- difficulties urinating.

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body, fainting or difficulties in swallowing
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite
- signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood
- chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath. This could be a sign of a serious condition with your heart.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients
Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20 mg.

Plus the following inactive ingredients,

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Microcrystalline cellulose
- Synthetic paraffin
- Macrogol 6000
- Polysorbate 80
- Crospovidone
- Sodium stearyl fumarate
- Purified talc
- Titanium dioxide
- Triethyl citrate
- Suglets sugar spheres 250/355 micrometres (maize starch and sucrose).
- Iron oxide red
- Iron oxide yellow

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Sponsor

Haleon
Sydney, NSW, Australia &
Auckland, New Zealand

AU: 1800 028 533
NZ: 0800 540 144

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 231439

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NPA018379

Pre-folding

500,0 mm

INTERLEAVED 2 OF 5 CODE REF. IS: XXXXXX

INTERLEAVED 2 OF 5 CODE REF. IS: XXXXXX

18 mm max

WYA0215

8,5 mm
1,5 mm

8,5 mm
1,5 mm

Scale 1:1

0 1 2 3 4 5
cm

2/5 code area reserved

Text Area

Cross Cutting

Dieline LINE

Ver.	Date	Reason for revision	Author	Note	Tecnical info
01	19 May 2011	New Drawing	A. Gaudio	Used for:	Scale: 1:1
02	10 Jan 2018	Eliminate read direction pharmacode	B. Bornago		Two side leaflet (front/back) dim. unfolded leaflet: 170 x 500 mm dim. folded leaflet: Refer to Material Spec
03	27 July 2023	Update info table	B. Bornago		

Artwork&Packaging APRILIA DEPT

Description: **Leaflet**

Drawing no.: **WYA0215**

APRILIA

Site Additional Artwork Information Panel

Varnish type: XXXXX

Reel unwind: XXXXX

V3 27 - Aug - 2025

Artwork Information Panel **HALEON**

Non Production Artwork [X] Production Artwork [ ]

Total Number of Colours including Varnish & Foils: 1

Black
1.

Total Special Finishes: 0

Studio Location: Asia

Component No: NPA018379	AWP No: TR3623983/C
Manufacturing Site: Aprilia	
Approving Market: Australia / New Zealand	
Technical Drawing No: WYA0215 v03	
Material Spec No: N/A	
Body Text Size: N/A	
Smallest Text Size: 8.0pt	
Electronic Verification Code: N/A	
Printer and User notes: N/A	

AWP_CHAMPS_2020_HALEON

Attachment 2

Nexium® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not use Nexium 24HR if you are experiencing unexplained weight loss, difficulty swallowing, persistent regurgitation of food or vomiting or vomiting of blood, severe or persistent diarrhoea, blood in the stools or symptoms of gastro-intestinal bleeding, except on medical advice.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn.

Do not take Nexium 24HR if you are pregnant or intend to become pregnant except on the advice of a doctor or pharmacist.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV.

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet.

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.
Do not take more than the recommended dose.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

500,0 mm

Scale 1:1

0 1 2 3 4 5
cm

2/5 code area reserved

Text Area

Cross Cutting

Dieline LINE

Ver.	Date	Reason for revision	Compiler	Note	Tecnical info	
01 02	19 May 2011 10 Jan 2018	New Drawing Eliminate read direction pharmacode	A. Gaudio B. Bornago		Scale: 1:1 Two side leaflet (front/rear) dim. spreaded leaflet: 170,0 x 500,0 mm dim. folded leaflet: 170,0 x 30,0 mm Pre-Folding at 250 mm	DTP ARTWORK APRILIA PLANT
					Description **Instruction Leaflet**	Drawing no. **WYA0215**

V1 26 - JUL - 2024

Artwork Information Panel HALEON

Non Production Artwork [X]	Production Artwork [ ]
Total Number of Colours including Varnish & Foils: 1	
1. Black	2. 3. 4. 5. 6.
7.	8. 9. 10. 11. 12.
Total Special Finishes: 0	

Component No: NPA016246	AWP No: **7764760**
Manufacturing Site: (Note: North American Artwork will have N/A in this field)	
Approving Market: Australia-AUS	
Technical Drawing No: WYA0215 v02	
Material Spec No: (Note: North American Artwork will have N/A in this field)	
Body Text Size: 9.0pt Smallest Text Size: 9.0pt Note: For North American Artwork, see Regulatory Spec box for this information)	
Electronic Verification Code:	
Printer and User notes:	

AIP_CHAMPS_2023_HALEON

10 mm
170,0 mm

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (Australia 13 11 26, or New Zealand 0800 764 766) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Side effects such as dizziness and visual disturbances may uncommonly occur. If affected, you should not drive or use machines.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth
- tiredness.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine
- difficulties urinating.

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body, fainting or difficulties in swallowing
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite
- signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood
- chest pain with light-headedness, sweating, dizziness or shoulder pain with shortness of breath. This could be a sign of a serious condition with your heart.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients
Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20 mg.

Plus the following inactive ingredients,

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Microcrystalline cellulose
- Synthetic paraffin
- Macrogol 6000
- Polysorbate 80
- Crospovidone
- Sodium stearyl fumarate
- Purified talc
- Titanium dioxide
- Triethyl citrate
- Suglets sugar spheres 250/355 micrometres (maize starch and sucrose).
- Iron oxide red
- Iron oxide yellow

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Pre-folding

Sponsor

Haleon
Sydney, NSW, Australia &
Auckland, New Zealand

AU: 1800 028 533
NZ: 0800 540 144

Australian Registration Number
AUST R 231439

This leaflet was prepared July 2024.

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62000000XXXXXX

Int. 2 of 5 : XXXXXX
18 mm max
Int. 2 of 5 : XXXXXX
WYA0215
8,5 mm
1,5 mm
8,5 mm
1,5 mm

Scale 1:1
cm 0 1 2 3 4 5

2/5 code area reserved
Text Area
Cross Cutting
Dieline LINE

Ver.	Date	Reason for revision	Compiler	Note	Tecnical info	
01 02	19 May 2011 10 Jan 2018	New Drawing Eliminate read direction pharmacode	A. Gaudio B. Bornago		Scale: 1:1 Two side leaflet (front/rear) dim. spreaded leaflet: 170,0 x 500,0 mm dim. folded leaflet: 170,0 x 30,0 mm Pre-Folding at 250 mm	DTP ARTWORK APRILIA PLANT
					Description **Instruction Leaflet**	Drawing no. **WYA0215**

V1
26 - JUL - 2024
Artwork Information Panel
HALEON

Non Production Artwork [X]
Production Artwork [ ]
Total Number of Colours including Varnish & Foils: 1
1. Black
Total Special Finishes: 0

Component No: NPA016246
AWP No: 7764760
Manufacturing Site:
(Note: North American Artwork will have N/A in this field)
Approving Market: Australia-AUS
Technical Drawing No: WYA0215 v02
Material Spec No:
(Note: North American Artwork will have N/A in this field)
Body Text Size: 9.0pt
Smallest Text Size: 9.0pt
(Note: For North American Artwork, see Regulatory Spec box for this information)
Electronic Verification Code:
Printer and User notes:

AIP_CHAMPS_2023_HALEON

Attachment 2



V3 07 - NOV - 2023	Artwork Information Panel	HALEON

Non Production Artwork		Production Artwork	X

Total Number of Colours including Varnish & Foils: 6

1. Cyan	2. Yellow	3. Black	4. PANTONE Rhodamine Red C	5. PANTONE 2607 C	6. Varnish - UV
7.	8.	9.	10.	11.	12.

Total Special Finishes: 2

Emboss	Emboss 2				

Component No:	AWP No:
62000000206379	7414241

Manufacturing Site: Aprilia
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: WYA0329 v03

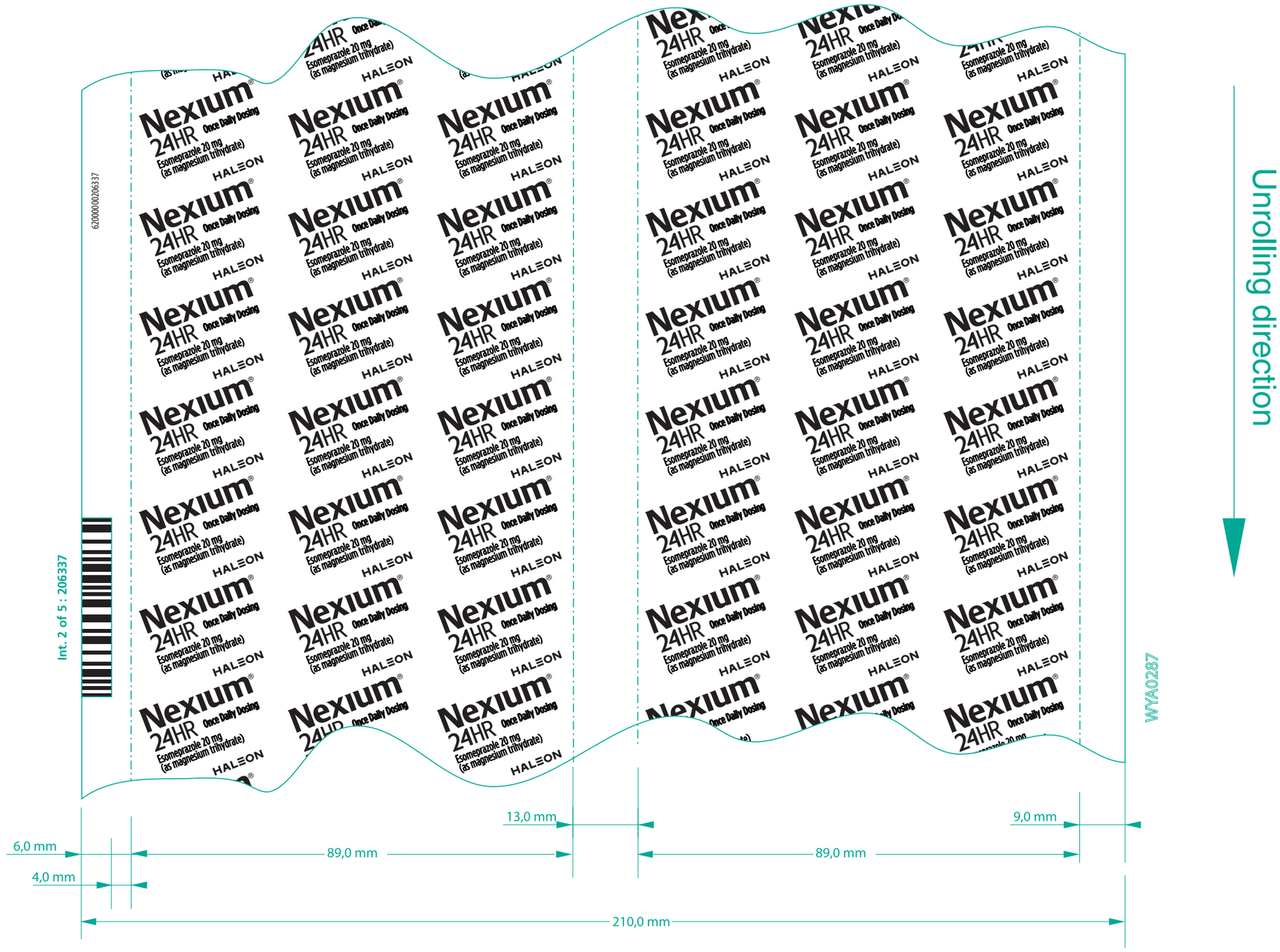
Material Spec No: TD: WYA0329 - SC: 1086 V.02 - Varnish: UV
(Note: North American Artwork will have N/A in this field)

Body Text Size: 6.0pt
Smallest Text Size: 4.0pt
(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

AIP_CHAMPS_2023_HALEON



V2
06 - NOV - 2023

Artwork Information Panel

HALEON

Non Production Artwork		Production Artwork	X

Component No:	AWP No:
62000000206337	7414244

Manufacturing Site: Aprilia
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: WYA0287 v02

Material Spec No: TD: WYA0287 - SC: 0684
(Note: North American Artwork will have N/A in this field)

Body Text Size: 6.0pt
Smallest Text Size: 6.0pt
(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

Total Number of Colours including Varnish & Foils: 1

70% 50% 20%					
1. Black	2.	3.	4.	5.	6.
7.	8.	9.	10.	11.	12.

Total Special Finishes: 0

AIP_CHAMPS_2023_HALEON

Nexium® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

What is in this leaflet

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This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

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There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not use Nexium 24HR if you are experiencing unexplained weight loss, difficulty swallowing, persistent regurgitation of food or vomiting or vomiting of blood, blood in the stools or symptoms of gastro-intestinal bleeding, except on medical advice.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn

Do not take Nexium 24HR if you are pregnant or intend to become pregnant except on the advice of a doctor or pharmacist.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

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2/5 code area reserved

Text Area

Cross Cutting

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Ver.	Date	Reason for revision	Compiler	Note	Tecnical info	
01 02	19 May 2011 10 Jan 2018	New Drawing Eliminate read direction pharmacode	A. Gaudio B. Bornago		Scale: 1:1 Two side leaflet (front/rear) dim. spreaded leaflet: 170,0 x 500,0 mm dim. folded leaflet: 170,0 x 30,0 mm Pre-Folding at 250 mm	DTP ARTWORK APRILIA PLANT
					Description **Instruction Leaflet**	Drawing no. **WYA0215**

V2 06 - NOV - 2023

Artwork Information Panel HALEON

Non Production Artwork ☐	Production Artwork X
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1. Black	2. 3. 4. 5. 6.
7.	8. 9. 10. 11. 12.
Total Special Finishes: 0	

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Manufacturing Site: Aprilia (Note: North American Artwork will have N/A in this field)	
Approving Market: Australia-AUS	
Technical Drawing No: WYA0215 v02	
Material Spec No: TD: WYA0215 - SC: 0032 (Note: North American Artwork will have N/A in this field)	
Body Text Size: 9.0pt Smallest Text Size: 9.0pt Note: For North American Artwork, see Regulatory Spec box for this information)	
Electronic Verification Code:	
Printer and User notes:	

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Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (Australia 13 11 26, or New Zealand 0800 764 766) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- “pins and needles”
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.
- Signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients
Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20 mg.

Plus the following inactive ingredients,

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Microcrystalline cellulose
- Synthetic paraffin
- Macrogol 6000
- Polysorbate 80
- Crospovidone
- Sodium stearyl fumarate
- Purified talc
- Titanium dioxide
- Triethyl citrate
- Suglets sugar spheres 250/355 micrometres (maize starch and sucrose).
- Iron oxide red
- Iron oxide yellow

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Pre-folding

Sponsor

Haleon
Sydney, NSW, Australia &
Auckland, New Zealand

AU: 1800 028 533
NZ: 0800 540 144

Australian Registration Number

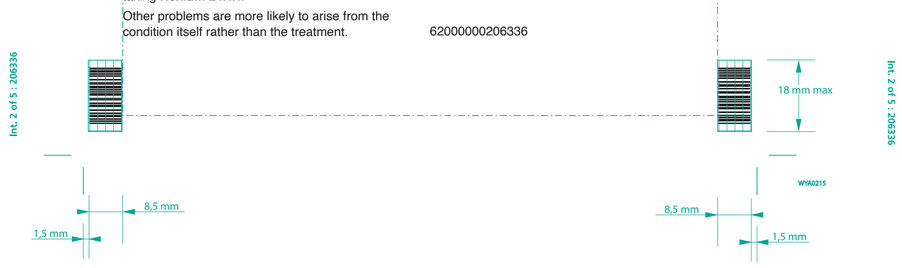
Nexium 24HR Once Daily Dosing
AUST R 231439

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Text Area

Cross Cutting

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Ver.	Date	Reason for revision	Compiler	Note	Tecnical info	
01 02	19 May 2011 10 Jan 2018	New Drawing Eliminate read direction pharmacode	A. Gaudio B. Bornago		Scale: 1:1 Two side leaflet (front/rear) dim. spreaded leaflet: 170,0 x 500,0 mm dim. folded leaflet: 170,0 x 30,0 mm Pre-Folding at 250 mm	DTP ARTWORK APRILIA PLANT
					Description **Instruction Leaflet**	Drawing no. **WYA0215**

V2
06 - NOV - 2023

Artwork Information Panel HALEON

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				62000000206336	7414245

Total Number of Colours including Varnish & Foils: 1

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7.	8.	9.	10.	11.	12.

Total Special Finishes: 0

Manufacturing Site: Aprilia
(Note: North American Artwork will have N/A in this field)

Approving Market: Australia-AUS

Technical Drawing No: WYA0215 v02

Material Spec No: TD: WYA0215 - SC: 0032
(Note: North American Artwork will have N/A in this field)

Body Text Size: 9.0pt
Smallest Text Size: 9.0pt
(Note: For North American Artwork, see Regulatory Spec box for this information)

Electronic Verification Code:

Printer and User notes:

AIP_CHAMPS_2023_HALEON

AUSTRALIAN PRODUCT INFORMATION

NEXIUM® 24HR Once Daily Dosing
(Esomeprazole magnesium trihydrate)

1. NAME OF THE MEDICINE

Esomeprazole magnesium trihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule or tablet of NEXIUM 24HR Once Daily Dosing (referred as NEXIUM 24HR elsewhere in this Product Information) contains esomeprazole magnesium trihydrate 22.3 mg (equivalent to esomeprazole 20 mg) as enteric-coated pellets.

Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer.

Excipient(s) with known effect:
Sucrose

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

NEXIUM 24HR 20 mg capsules are approximately 11 x 5 mm with a clear body, and an amethyst cap imprinted with “NEXIUM 20 MG” in white. The capsule has a yellow centre band, and contains yellow and purple enteric coated pellets.

NEXIUM 24HR 20 mg tablets are light pink, oblong, biconvex, film-coated tablet engraved “20 mg” on one side and “A/EH” on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

NEXIUM 24HR is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults
For symptomatic treatment of gastro-oesophageal reflux disease (GORD), take 1 capsule (20 mg) or tablet (20 mg) once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persist or worsen while taking this course, or if symptoms persist or recur within two weeks of completing the course.

Children below the age of 18 years:
NEXIUM 24HR is not intended for use in children under the age of 18.

Method of administration
NEXIUM 24HR capsules or tablets should be swallowed whole with liquid. The capsules or tablets must not be chewed, crushed or opened.

If required, the NEXIUM 24HR tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Dosage adjustment

Geriatrics
Dose adjustment is not required in the elderly.

Hepatic impairment
Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM 24HR should not be exceeded (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Renal impairment
Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

4.3. CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, Effects of esomeprazole on other drugs).

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with all antisecretory agents, in the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases

gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

CYP2C19 enzyme
Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Hypomagnesaemia
Hypomagnesaemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesaemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically during PPI treatment.

Hypomagnesaemia may lead to hypocalcaemia and/or hypokalaemia (see section 4.8 Adverse Effects (Undesirable Effects)).

Gender
Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM 24HR.

Use in hepatic impairment
The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in renal impairment
No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for

the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Paediatric use
NEXIUM 24HR is not intended for use in children under the age of 18.

Use in the elderly
The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Effect on laboratory tests
Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5 to 14 days before CgA measurement and that measurements should be repeated if levels have not normalised by this time.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Other drugs that affect esomeprazole

Clarithromycin
Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride
In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cilostazol
Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively (see Section 4.3 CONTRAINDICATIONS).

Citalopram, Clomipramine and Imipramine
Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel
Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel + the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam
Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs
Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any

clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin
Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin
Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus
Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate
When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs
Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs is not recommended.

Medicinal products with pH dependent absorption
The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to

30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxycillin or quinidine
Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy - Category B3
For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM 24HR should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation
It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM 24HR should not be used during breast feeding.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Esomeprazole is not likely to affect the ability to drive or use machines.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NEXIUM 24HR is well tolerated.

Clinical trials and post-marketing data
The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders
Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders
Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders
Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; Hypomagnesaemia may result in hypokalaemia and/or hypocalcaemia.

Psychiatric disorders
Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders
Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances
Rare: blurred vision

Ear and labyrinth disorders
Uncommon: vertigo

Respiratory, thoracic mediastinal disorders
Rare: bronchospasm

Gastrointestinal disorders
Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis
Frequency not known: Withdrawal of long-term PPI therapy can lead to aggravation of acid-related symptoms and may result in rebound acid hypersecretion.

Hepatobiliary disorders
Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders
Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Musculoskeletal, connective tissue and bone disorders
Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders
Very rare: Interstitial nephritis

Reproductive system and breast disorders
Very rare: gynaecomastia

General disorders and administration site conditions
Rare: malaise, hyperhidrosis

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9. OVERDOSE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful.

Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised. No specific antidote is known.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
NEXIUM 24HR (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H+, K+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H+, K+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five.

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	**% time intragastric pH > 4**	**p-value**
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001

	n	% time intragastric pH > 4	p-value
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition
During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Clinical trials

Symptomatic treatment of GORD in patients with normal endoscopy
At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or H. pylori status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

5.2. PHARMACOKINETIC PROPERTIES

Absorption
Esomeprazole is acid labile and is administered orally as enteric coated pellets in capsules or tablets. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo*

conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20 mg esomeprazole and increases to 68% after repeated once daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution
The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism
Esomeprazole is completely metabolised by the cytochrome P-450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion
The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM 24HR is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity
Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under *in vivo* conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Carcinogenicity
Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H2-receptor antagonists and by partial fundectomy.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

NEXIUM 24HR capsules:

Capsule content
Glyceryl monostearate
Hyprolose
Hypromellose
Magnesium stearate
Methacrylic acid copolymer
Polysorbate 80
Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
Purified Talc
Triethyl citrate
Titanium dioxide (E171)
Carmine (E120)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)

Capsule shell
Gelatin
Erythrosine
Indigo carmine (E132)
Allura red AC (E129)

Printing ink
Povidone
Propylene glycol
Shellac
Sodium hydroxide
Titanium dioxide (E171)

Band
Gelatin
Iron oxide yellow (E172)

NEXIUM 24HR tablets:
Glyceryl monostearate
Hyprolose
Hypromellose
Magnesium stearate
Methacrylic acid copolymer
Microcrystalline cellulose
Synthetic paraffin
Macrogol 6000
Polysorbate 80
Crospovidone
Sodium stearylfumarate
Purified talc
Triethyl citrate
Sugar spheres (maize starch and sucrose)
Titanium dioxide
Iron oxide red CI77491
Iron oxide yellow CI77492

6.2. INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3. SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

Store in the original package in order to protect from moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

NEXIUM 24HR capsules:

Container type
High-density polyethylene (HDPE) bottle with an induction seal closure and child resistant closure containing 14 capsules. The bottle also contains a sealed container with silica gel desiccant.

Pack size
NEXIUM 24HR capsules are available in a bottle of 14 capsules.

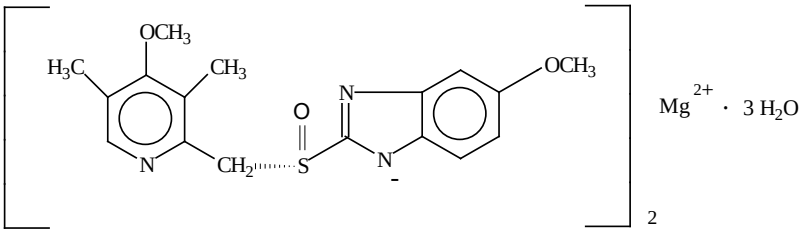
NEXIUM 24HR tablets:
NEXIUM 24HR tablets are available in blister pack of 7 and 14 tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. PHYSICOCHEMICAL PROPERTIES

Chemical structure
The chemical name of esomeprazole magnesium trihydrate is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate.



Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$
Molecular weight: 767.2 (trihydrate)

CAS number
217087-09-7

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 2 – Pharmacy Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

8. SPONSOR

GlaxoSmithKline Consumer Healthcare Australia Pty Ltd trading as Haleon

Level 48, 8 Parramatta Square,

10 Darcy Street, Parramatta NSW 2150

9. DATE OF FIRST APPROVAL

NEXIUM 24HR capsules: 15 April 2019
NEXIUM 24HR tablets: 04 December 2014

10. DATE OF REVISION

19 September 2022

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Summary table of changes

Sections changed	Summary of new information
4.4	Addition of hypomagnesaemia
8	Update to sponsor name and address

NEXIUM® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux. This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week. **Nexium 24HR** is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not use Nexium 24HR if you are experiencing unexplained weight loss, difficulty swallowing, persistent regurgitation of food or vomiting of blood, blood in the stools or symptoms of gastro-intestinal bleeding, except on medical advice.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn

Do not take Nexium 24HR if you are pregnant or intend to become pregnant except on the advice of a doctor or pharmacist. Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

- atazanavir - medicine used to treat viral infections such as HIV
- cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include**:**

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26, or New Zealand 0800 764 766) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking NEXIUM 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist or that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body

- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.
- Signs of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hand, feet or voice. Low magnesium can lead to low calcium and/or low potassium levels in blood.

These are very serious side effects. You may need urgent medical treatment or hospitalisation. Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A /EH on the other.

Ingredients

Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients,

- Glyceryl monostearate
- Hyprolose
- Hypromellose
- Magnesium stearate
- Methacrylic acid copolymer
- Microcrystalline cellulose
- Synthetic paraffin
- Macrogol 6000
- Polysorbate 80
- Crospovidone
- Sodium stearyl fumarate
- Purified Talc
- Titanium dioxide
- Triethyl citrate
- Suglets sugar spheres 250/355 micrometres (sucrose and maize starch)
- Iron oxide red
- Iron oxide yellow

No added gluten.

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Sponsor

GlaxoSmithKline Consumer Healthcare trading as Haleon, Sydney, NSW, Australia

AU: 1800 028 533

Australian Registration Number

Nexium 24HR Once Daily Dosing

AUST R 231439

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Attachment 2



SGS The Maltings	Product Name: Nexium 24HR 7's (S2) – AUS				
Cyan, PANTONE Rhodamine, Yellow, Black, PANTONE 2607 C, Gloss Varnish; Emboss, Emboss 2nd Level, Gloss Varnish Free, Pharmacode, Technical, Dieline				Prepared by s.22	Date 07/09/2015
Item Code CA3694-00	Dieline W195	Date 07/09/2015		Checked by	Date
PAR 2015-0027824	Pharma Code 5615	Proof No 1			
Market AUSTRALIA - AU	Standard Colour 1086 v02	MySGS Ref No 669126-1			

Please ensure artwork is checked with Overprint Preview turned on

CUSTOMER APPROVAL SECTION	Prepared by	Date

Barcode Type(s): EAN-13, Pharma

X-Height Rule: Y

Job Name:	76600 Nexium Australia 7s S2 carton FA
Client:	PFIZER
DBG Job No.:	76600 Date: 20.03.2018
Item Code:	WC1533 Package Code: NA
Proof No.:	4
Dimensions:	179.0mm wide x 204.3mm deep (FLAT CARTON)

Colours: CYK, PANTONE 2607 C, PANTONE Rhodamine Red, Gloss Varnish, Embossing, Embossing 2nd Level

PLEASE EXAMINE THIS PROOF CAREFULLY
Whilst all care and attention is taken when preparing your design, it is requested you check all details carefully. It is the responsibility of the client to ensure that all details shown are correct and ready for production. The client is responsible for any errors in the design, which are not corrected by the client, before the design is completed. **This is a proof, the colours and screen densities used in the proofing process provide a representation only, the final colour(s) may vary from this proof.**

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SGS The Maltings	Product Name: **Nexium 24HR tablets 14's**				
Black, Cyan, Gloss Varnish, PANTONE 2607 C, PANTONE Rhodamine Red C, Yellow; Pharmacode, Glossy Varnish Free, Embossed Level 2, Emboss, Technical, Dieline				Prepared by: s.22	Date: 12/05/2016
Item Code: CA3412-02	Dieline: W196	Date: 12/05/2016			
PAR: 2016-0001614	Pharma Code: 5617	Proof No: 1		Checked by	Date
Market: AUSTRALIA - AU	Standard Colour: 1086 v.02	MySGS No: 756184-0			

Please ensure artwork is checked with Overprint Preview turned on

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CUSTOMER APPROVAL SECTION

Barcode Type(s): EAN 13, Pharma

X-Height Rule: Y

Job Name:	76600 Nexium Australia 14s S2 carton FA-V2
Client:	PFIZER
DBG Job No.:	76600 Date: 20.03.2018
Item Code:	WC1534 Package Code: NA
Proof No.:	5
Dimensions:	195.0mm wide x 216.3mm deep (FLAT CARTON)

Colours: CYK, PANTONE 2607 C, PANTONE Rhodamine Red, Gloss Varnish, Embossing, Embossing 2nd Level

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Nexium 24HR

Once Daily Dosing
Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant unless your doctor says so.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

Text

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

Front side

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Pre-folding

Job Name:	76600 NEXIUM AUSTRALIA S2 CMI		
Client:	PFIZER		
DBG Job No.:	76600	Date:	20/03/2018
Item Code:	WI1011	Package Code:	
Proof No.:	3		
Dimensions:	170 W x 500 H mm		
Colours:	PANTONE 2607		

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Pharmacode Travel direction

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- “pins and needles”
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients
Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients,

- Glyceryl monostearate (E 471)
- Hydroxypropyl cellulose
- Hypromellose
- Magnesium stearate (E 572)
- Methacrylic acid copolymer
- Microcrystalline cellulose (E 460).
- Paraffin synthetic
- Macrogol 6000
- Polysorbate 80 (E 433)
- Crospovidone
- Sodium stearyl fumarate
- Purified talc (E 553(b))
- Titanium dioxide (E 171)
- Triethyl citrate
- Sugar spheres (maize starch and sucrose).

The tablets are coloured with iron oxide red CI77491 and iron oxide yellow CI77492

No added gluten.

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Sponsor

Pfizer Australia Pty Limited
38-42 Wharf Rd,
West Ryde NSW 2114

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 231439

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WI1011

Text

Rear side

Pre-folding

18 mm max

Pharmacode Travel direction

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NEXIUM® 24HR Once Daily Dosing

esomeprazole magnesium trihydrate

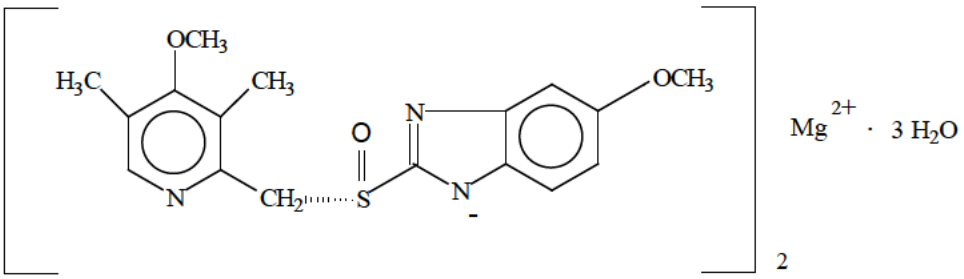
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this Product Information), is a proton pump inhibitor. The active ingredient in NEXIUM 24HR is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 24HR 20 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The tablets are coloured with titanium dioxide, iron oxide red CI77491 and iron oxide yellow CI77492.

PHARMACOLOGY

Nexium 24HR (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2 Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20mg esomeprazole and increases to 68% after repeated once daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM 24HR is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

INDICATIONS

NEXIUM 24HR is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM 24HR.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under in vivo conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM 24HR should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM 24HR should not be used during breast feeding

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Other drugs that affect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel+the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxycillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5 to 14 days before CgA measurement and that measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM 24HR is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM 24HR tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Adults

For symptomatic treatment of gastro-oesophageal reflux disease (GORD), take 1 tablet (20mg) once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persists or worsens while taking this course, or if symptoms persist or recur within two weeks of completing the course.

Children below the age of 18 years:

NEXIUM 24HR is not intended for use in children under the age of 18.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM 24HR should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM 24HR tablets should be stored below 25°C.

Nexium 24HR 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 24HR tablets are available in pack sizes of 7 and 14 tablets.

NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Limited
38-42 Wharf Road
WEST RYDE, NSW 2114

POISON SCHEDULE OF THE MEDICINE

S2 – Pharmacy Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 4 December 2014

DATE OF MOST RECENT AMENDMENT: 15 September 2017

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SGS The Maltings	Product Name: Nexium 24HR tablets 14's				
Black, Cyan, Gloss Varnish, PANTONE 2607 C, PANTONE Rhodamine Red C, Yellow; Pharmacode, Glossy Varnish Free, Embossed Level 2, Emboss, Technical, Dieline				Prepared by	Date 12/05/2016
Item Code	CA3412-02	Dieline	W196	Date	12/05/2016
PAR	2016-0001614	Pharma Code	5617	Proof No	1
Market	AUSTRALIA - AU	Standard Colour	1086 v.02	MySGS No	756184-0
				Checked by	Date

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Overprint correctly set

CUSTOMER APPROVAL SECTION

OM-2017-00837-1

Barcode Type(s): EAN 13, Pharma

X-Height Rule: Y

Job Name:	74396 Nexium Australia 14s S2 carton FA
Client:	PFIZER
DBG Job No.:	74396 Date: 19.01.2017
Item Code:	WCXXXX Package Code: NA
Proof No.:	2
Dimensions:	195.0mm wide x 216.3mm deep (FLAT CARTON)

Colours: CYK, PANTONE 2607 C, PANTONE Rhodamine Red, Gloss Varnish, Embossing, Embossing 2nd Level

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NEXIUM® 24HR Once Daily Dosing

esomeprazole magnesium trihydrate

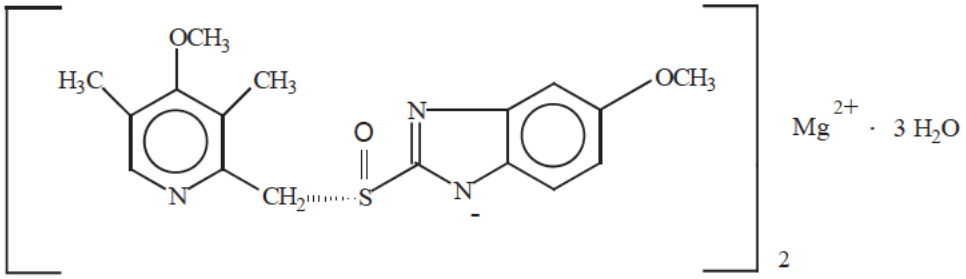
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this Product Information), is a proton pump inhibitor. The active ingredient in NEXIUM 24HR is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 24HR 20 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The tablets are coloured with titanium dioxide, iron oxide red CI77491 and iron oxide yellow CI77492.

PHARMACOLOGY

Nexium 24HR (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20mg esomeprazole and increases to 68% after repeated once daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM 24HR is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

INDICATIONS

NEXIUM 24HR is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM 24HR.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under in vivo conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM 24HR should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM 24HR should not be used during breast feeding

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Other drugs that affect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel+the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxycillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5 to 14 days before CgA measurement and that measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM 24HR is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM 24HR tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Adults

For symptomatic treatment of gastro-oesophageal reflux disease (GORD), take 1 tablet (20mg) once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persists or worsens while taking this course, or if symptoms persist or recur within two weeks of completing the course.

Children below the age of 18 years:

NEXIUM 24HR is not intended for use in children under the age of 18.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM 24HR should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM 24HR tablets should be stored below 25°C.

Nexium 24HR 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 24HR tablets are available in pack sizes of 7 and 14 tablets.

NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Limited
38-42 Wharf Road
WEST RYDE, NSW 2114

POISON SCHEDULE OF THE MEDICINE

S2 – Pharmacy Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 7 days' supply.

S3 – Pharmacist Only Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days' supply except when included in Schedule 2.~~**S3 – Pharmacist Only Medicine** when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply.~~

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): 4 December 2014

DATE OF MOST RECENT AMENDMENT:

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Attachment 3



SGS The Maltings	Product Name: Nexium 24HR 7's (S2) – AUS		
Item Code CA3694-00	Dieline W195	Date 07/09/2015	Prepared by s.22 Date 07/09/2015
PAR 2015-0027824	Pharma Code 5615	Proof No 1	Checked by Date
Market AUSTRALIA – AU	Standard Colour 1086 v02	MySGS Ref No 669126-1	

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Warning: Overprint not correctly set

CUSTOMER APPROVAL SECTION	Prepared by	Date

Barcode Type(s): EAN-13, Pharma

X-Height Rule: Y

Nexium 24HR

Once Daily Dosing
Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet)**. It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking **Nexium 24HR** against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

There is no evidence that **Nexium 24HR** is addictive.

Deleted:
"Nexium 24HR is available only from your pharmacist"

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant unless your doctor says so.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

If you purchased the pack containing 7 days' supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor.

Added:
"If you purchased the pack containing 7 day's supply and you need to take for longer than 7 days, ask your pharmacist for advice. Do not take beyond 14 days without consulting your doctor"

Deleted:
"You should not take it for more than 14 days unless directed by your doctor."

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients
Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients:

- Glyceryl monostearate (E 471)
- Hydroxypropyl cellulose
- Hypromellose
- Magnesium stearate (E 572)
- Methacrylic acid copolymer
- Microcrystalline cellulose (E 460).
- Paraffin synthetic
- Macrogol 6000
- Polysorbate 80 (E 433)
- Crospovidone
- Sodium stearyl fumarate
- Purified talc (E 553(b))
- Titanium dioxide (E 171)
- Triethyl citrate
- Sugar spheres (maize starch and sucrose).

The tablets are coloured with iron oxide red CI77491 and iron oxide yellow CI77492

Nexium 24HR tablets do not contain gluten.

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Sponsor

Pfizer Australia Pty Limited
38-42 Wharf Rd,
West Ryde NSW 2114

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 231439

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CI3261-00

Component Travel Direction

Component Travel Direction

SGS The Netherlands

Product Name: Nexium 24HR 7's (S2) – AUS

Item Code	CI3261-00	Dieline	170 x 500 mm	Date	15/09/2015
PAN	2015-0027424	Pharma Code	1023	Proof No	2
Market	AUSTRALIA - AU	Standard Colour	1334	MySGS No	669138-0

Prepared by: s.2 Date: 15/09/2015
Checked by: Date:

Please ensure artwork is checked with Overprint Preview turned on

Warning: Overprint not correctly set

CUSTOMER APPROVAL SECTION

Barcode Type(s): Pharma, QR

X-Height Rule: N

Attachment 2

PROPOSED



Emboss -
Full size file on Emboss layer*
* There are two levels of Embossing.



a 4/106 grose street, parramatta nsw 2150
p 02 9630 1733 f 02 9630 1930
e info@dbgraphics.com.au
w www.dbgraphics.com.au

Name:	71184 Nexium Australia 7s S3 carton new FA
DBG Job No:	71184 Previous DBG Job No: 69210
Item Code:	
Date:	22/07/2015
Proof No.:	1
Dimensions:	75.0 x 115.0 x 22.0mm (Flat dimensions 179.0 x 204.3mm)
Colours:	

PROCESS CYAN* | PANTONE Rhodamine Red C | PROCESS YELLOW | PROCESS BLACK | PANTONE 2607 C | GLOSS VARNISH | Emboss | Emboss 2nd Level

Printer MUST use Pantone Rhodamine Red C in place of all Process Magenta.
***Printer MAY also use Pantone Process Blue C in place of all Process Cyan to match standard.**

PLEASE EXAMINE THIS PROOF CAREFULLY
Whilst all care and attention is taken when preparing your design, it is requested you check all details carefully. It is the responsibility of the client to ensure that all details shown are correct and ready for production. The client is responsible for any errors in the design, which are not corrected by the client, before the design is completed.
This is a proof, the colours and screen densities used in the proofing process provide a representation only, the final colour(s) may vary from this proof.

Attachment 2

PROPOSED



Emboss -
Full size file on Emboss layer*
* There are two levels of Embossing.



a 4/106 grose street, parramatta nsw 2150
p 02 9630 1733 f 02 9630 1930
e info@dbgraphics.com.au
w www.dbgraphics.com.au

Name:	71184 Nexium Australia 14s S3 carton new FA
DBG Job No:	71184 Previous DBG Job No: 69210
Item Code:	
Date:	22/07/2015
Proof No.:	1
Dimensions:	75.0 x 115.0 x 22.0mm (Flat dimensions 179.0 x 204.3mm)
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Attachment 4

PROPOSED

Nexium 24HR

Once Daily Dosing
Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium® 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet).** It does not contain all the information that is known about **Nexium 24HR.**

It does not take the place of talking to your pharmacist or doctor.

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If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux.

This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week.

Nexium 24HR is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

Nexium 24HR is available only from your pharmacist.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not intended for use in children under 18 years of age.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver
- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant unless your doctor says so.

Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take **Nexium 24HR** while you are pregnant. It may affect your baby.

Do not take Nexium 24HR if you are breastfeeding. Ask your doctor for more information.

It is not known if **Nexium 24HR** is excreted in breast-milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

atazanavir - medicine used to treat viral infections such as HIV

cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles.

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with **Nexium 24HR**. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

You should not take it for more than 14 days unless directed by your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Text

Front side

Pre-folding

<dbg> <davidbrowngraphics> design communication

a 4/106 grose street, parramatta nsw 2150
p 02 9630 1733 f 02 9630 1930
e info@dbgraphics.com.au
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Name:	71184 Nexium Australia S3 CMI
DBG Job No:	71184 Previous DBG Job No: 69210
Item Code:	
Date:	23/7/2015
Proof No.:	2
Dimensions:	170 W x 500 H mm
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Pharmacode Travel direction

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking Nexium 24HR

Things you must do

If you are about to be started on any new medicine, tell your pharmacist, doctor or dentist that you are taking Nexium 24HR.

Tell all pharmacists, doctors and dentists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

These are very serious side effects. You may need urgent medical treatment or hospitalisation.

Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients
Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients,

- Glyceryl monostearate (E 471)
- Hydroxypropyl cellulose
- Hypromellose
- Magnesium stearate (E 572)
- Methacrylic acid copolymer
- Microcrystalline cellulose (E 460).
- Paraffin synthetic
- Macrogol 6000
- Polysorbate 80 (E 433)
- Crospovidone
- Sodium stearyl fumarate
- Purified talc (E 553(b))
- Titanium dioxide (E 171)
- Triethyl citrate
- Sugar spheres (maize starch and sucrose).

The tablets are coloured with iron oxide red CI77491 and iron oxide yellow CI77492

Nexium 24HR tablets do not contain gluten.

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Sponsor

Pfizer Australia Pty Limited
38-42 Wharf Rd,
West Ryde NSW 2114

Australian Registration Number

Nexium 24HR Once Daily Dosing
AUST R 231439

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Text

Rear side

Pre-folding

18 mm max

Pharmacode Travel direction

Pharma code area reserved

WYA0215

71184 Nexium Australia S3 CMI.indd 2 23/07/15 10:08 AM

Attachment 2

NEXIUM® 24HR Once Daily Dosing

esomeprazole magnesium trihydrate

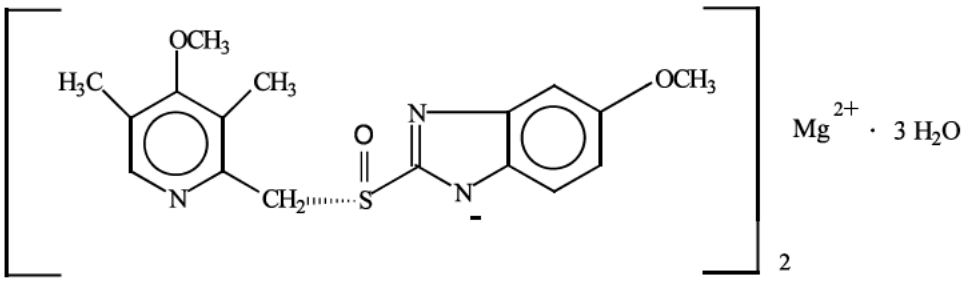
MULTIPLE UNIT PELLET SYSTEM

PRODUCT INFORMATION

NAME OF THE MEDICINE

NEXIUM 24HR Once Daily Dosing (referred as Nexium 24HR elsewhere in this Product Information), is a proton pump inhibitor. The active ingredient in NEXIUM 24HR is esomeprazole magnesium trihydrate, a substituted benzimidazole. Esomeprazole is the S-isomer of omeprazole. It is optically stable *in vivo*, with negligible conversion to the R-isomer. The chemical name is di-(S)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium salt trihydrate

The chemical structure of esomeprazole magnesium trihydrate is:



CAS number: 217087-09-7

Molecular formula: $C_{34}H_{36}N_6O_6S_2Mg.3H_2O$

Molecular weight: 767.2 (trihydrate)

DESCRIPTION

The Nexium 24HR 20 mg tablets are comprised of enteric coated pellets containing esomeprazole (as magnesium trihydrate). The tablets contain the following inactive ingredients: glyceryl monostearate, hydroxypropylcellulose, hypromellose, magnesium stearate, methacrylic acid copolymer, cellulose microcrystalline, paraffin synthetic, macrogol 6000, polysorbate 80, crospovidone, sodium stearylfumarate, talc, triethyl citrate and sugar spheres (maize starch and sucrose). The tablets are coloured with titanium dioxide, iron oxide red CI77491 and iron oxide yellow CI77492.

PHARMACOLOGY

Nexium 24HR (esomeprazole magnesium trihydrate) reversibly reduces gastric acid secretion by specifically inhibiting the gastric enzyme H^+, K^+-ATPase proton pump in the parietal cell. Both the R- and S-isomer of omeprazole have similar pharmacodynamic activity. In humans, acid control with esomeprazole is dose dependent and is significantly greater, more sustained and less variable compared to that obtained with equal doses of omeprazole.

Esomeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the secretory canaliculi of the parietal cell, where it inhibits the enzyme H^+, K^+-ATPase (the acid pump) and inhibits both basal and stimulated acid secretion.

Effect on gastric acid secretion

After oral dosing with esomeprazole 20 mg and 40 mg the onset of effect occurs within one hour. After repeated administration with 20 mg esomeprazole once daily for five days, mean peak acid output after pentagastrin stimulation is decreased 90% when measured 6-7 hours after dosing on day five

After five days of oral dosing with 20 mg and 40 mg of esomeprazole, intragastric pH above 4 was maintained for a mean time of 13 hours and 17 hours, respectively over 24 hours in symptomatic GORD patients. The corresponding time for omeprazole 20 mg of 10 hours was significantly shorter. In this study plus another, the percentage of GORD patients maintaining an intragastric pH above 4 for at least 8, 12 and 16 hours are tabulated below.

Table 1 % GORD patients with intragastric pH >4 for at least 8, 12 and 16 hours

		% GORD patients with intragastric pH >4 for at least:		
Population	**Study drug**	**8 hours**	**12 hours**	**16 hours**
GORD (n=36)	Omeprazole 20 mg	67%	45%	14%
	Esomeprazole 20 mg	76%	54%	24%
	Esomeprazole 40 mg	97%	92%	56%

In vivo results demonstrate that acid control with esomeprazole is dose dependent and that it is significantly greater, more sustained and less variable compared to an equal dose of the racemate.

Using AUC as a surrogate parameter for plasma concentration, a relationship between inhibition of acid secretion and exposure has been shown.

A 6-way crossover study was conducted to investigate the dose response relationship assessed by intragastric pH monitoring after repeated once daily oral doses of 20, 40 and 80 mg of esomeprazole and 20, 40 and 80 mg of pantoprazole in symptomatic GORD patients. Results are provided in Table 2.

Table 2 **Means and mean differences in percentage of time with intragastric pH > 4 on Day 5 following repeated once daily administration of 20, 40 and 80 mg esomeprazole and pantoprazole in symptomatic GORD patients.**

	n	% time intragastric pH > 4	p-value
Esomeprazole 20 mg	35	46.97	
Pantoprazole 20 mg	35	28.75	
Esomeprazole 20 mg - Pantoprazole 20 mg		18.23	<0.0001
Esomeprazole 20 mg	35	47.41	
Pantoprazole 40 mg	35	37.59	
Esomeprazole 20 mg - Pantoprazole 40 mg		9.83	0.0003
Esomeprazole 40 mg	35	59.01	
Pantoprazole 40 mg	35	37.73	
Esomeprazole 40 mg - Pantoprazole 40 mg		21.27	<0.0001
Esomeprazole 40 mg	36	58.35	
Pantoprazole 80 mg	36	44.22	
Esomeprazole 40 mg - Pantoprazole 80 mg		14.13	<0.0001
Esomeprazole 80 mg	36	65.69	
Pantoprazole 80 mg	36	43.58	
Esomeprazole 80 mg - Pantoprazole 80 mg		22.12	<0.0001

Other effects related to acid inhibition

During treatment with antisecretory agents serum gastrin increases in response to decreased acid secretion.

An increased number of ECL cells possibly related to the increased serum gastrin levels, have been observed in some patients during long term treatment with esomeprazole.

During long-term treatment with antisecretory drugs gastric glandular cysts have been reported to occur. These changes are a physiological consequence of pronounced inhibition of acid secretion, are benign and appear reversible.

Pharmacokinetics

Absorption

Esomeprazole is acid labile and is administered orally as enteric coated pellets in tablets. The enteric coating film, protecting the esomeprazole magnesium trihydrate, dissolves at a pH above 5.5. Hence esomeprazole magnesium trihydrate is not released until the pellets are emptied into the duodenum.

Once esomeprazole magnesium trihydrate dissolves in this near neutral environment, the esomeprazole ion transforms to its neutral form and is absorbed as such. *In vivo* conversion to the R-isomer is negligible. Absorption is rapid with peak plasma levels of esomeprazole occurring approximately 1 to 2 hours after the dose. The absolute bioavailability is 50% after a single dose of 20mg esomeprazole and increases to 68% after repeated once daily administration.

Food intake both delays and decreases the absorption of esomeprazole although this has no significant influence on the effect of esomeprazole on intragastric acidity.

Distribution

The apparent volume of distribution at steady state in healthy subjects is approximately 0.22 L/kg body weight. Esomeprazole is 97% protein bound.

Metabolism

Esomeprazole is completely metabolised by the cytochrome P450 system (CYP450). The intrinsic clearance of esomeprazole (S-isomer) is one third of that of the R-isomer, resulting in a higher AUC with less inter-individual variation compared to the racemate. The major part of the metabolism of esomeprazole is dependent on the polymorphic CYP2C19, responsible for the formation of the hydroxy- and desmethyl metabolites of esomeprazole. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of esomeprazole sulphone, the main metabolite in plasma.

The parameters below reflect mainly the pharmacokinetics in individuals with a functional CYP2C19 enzyme, extensive metabolisers.

Total plasma clearance is about 17 L/h after a single dose and about 9 L/h after repeated administration. The plasma elimination half-life is about 1.3 hours after repeated once-daily dosing. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a non-linear dose-AUC relationship after repeated administration. This time- and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. Esomeprazole is completely eliminated from plasma between doses with no tendency for accumulation during once-daily administration.

Excretion

The major metabolites of esomeprazole have no effect on gastric acid secretion. Almost 80% of an oral dose of NEXIUM 24HR is excreted as metabolites in the urine, the remainder in the faeces. Less than 1% of the parent drug is found in urine.

CLINICAL TRIALS

Symptomatic treatment of GORD in patients with normal endoscopy

At the time of registration, five randomised, double-blind controlled clinical trials (n=3,362) were evaluated to assess the efficacy of esomeprazole in the complete resolution of heartburn at 4 weeks comparing esomeprazole 20 mg or 40 mg with omeprazole 20 mg or placebo. Study B7 was a dose-finding study, two studies compared esomeprazole 40 mg and omeprazole 20 mg (B8 and B9), and two compared esomeprazole 20 mg, 40 mg and placebo (B16 and B17).

There were no apparent differences in any of the studies between population subsets based on gender, age, race or *H. pylori* status in the proportion of patients with complete resolution of heartburn by treatment. The proportion of patients with complete resolution of heartburn at 4 weeks in studies B7, B8 and B9 (n=2,645), independent of treatment, was approximately 60%. There was no statistically significant difference between any of the treatment groups with regard to complete resolution of heartburn at 2 weeks or 4 weeks.

In studies B16 and B17 the proportion of patients (n=717) with complete resolution of heartburn at 4 weeks was significantly higher for esomeprazole 20 mg and 40 mg compared to placebo.

INDICATIONS

NEXIUM 24HR is indicated for the symptomatic relief of frequent heartburn, acid regurgitation and other symptoms associated with gastro-oesophageal reflux disease (GORD).

CONTRAINDICATIONS

Known hypersensitivity to esomeprazole, substituted benzimidazoles or any other constituents of the formulation.

Esomeprazole like other proton pump inhibitors should not be administered with atazanavir (refer Effects of esomeprazole on other drugs)

Esomeprazole, an inhibitor of CYP2C19, is contraindicated in patients taking cilostazol.

PRECAUTIONS

As with all antisecretory agents, the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with esomeprazole may alleviate symptoms and delay diagnosis.

Decreased gastric acidity due to any means including proton pump inhibitors, increases gastric counts of bacteria normally present in the gastrointestinal tract. Treatment with proton pump inhibitors may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter* and, in hospitalised patients, possibly also *Clostridium difficile*.

Special patient populations

CYP2C19 enzyme

Approximately 3% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is most likely catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers). Mean plasma concentrations were increased by about 60%. These findings have no implications for the dosage of esomeprazole. In case of clopidogrel, a prodrug which is transformed into its active metabolite via CYP2C19, the plasma concentrations of the active metabolite may be decreased.

Elderly

The metabolism of esomeprazole is not significantly changed in elderly subjects (71-80 years).

Gender

Following a single dose of 40 mg esomeprazole the mean area under the plasma-concentration-time curve is approximately 30% higher in females than in males. No gender difference is seen after repeated once-daily administration. These findings have no implications for the dosage of NEXIUM 24HR.

Hepatic insufficiency

The metabolism of esomeprazole in patients with mild to moderate liver dysfunction (Child Pugh A or B) may be impaired, however no dose adjustment is required. The metabolic rate is decreased in patients with severe liver dysfunction (Child Pugh C) resulting in a doubling of the area under the plasma concentration-time curve for esomeprazole. Therefore, a maximum of 20 mg should not be exceeded in patients with severe dysfunction. Esomeprazole or its major metabolites do not show any tendency to accumulate with once daily dosing (see DOSAGE AND ADMINISTRATION).

Renal impairment

No studies have been performed in patients with decreased renal function. Since the kidney is responsible for the excretion of the metabolites of esomeprazole but not for the elimination of the parent compound, the metabolism of esomeprazole is not expected to be changed in patients with impaired renal function.

Carcinogenicity

Preclinical bridging studies between the enantiomer esomeprazole and the racemate (omeprazole) showed that these compounds are pharmacologically and toxicologically similar at equivalent systemic exposure. Thus, the extensive preclinical database for omeprazole is also relevant for the safety assessment of esomeprazole.

No carcinogenicity studies have been conducted on esomeprazole. However, omeprazole (the racemate) produced enterochromaffin-like (ECL) cell hyperplasia and gastric carcinoids in rats. In a 104-week study in rats, carcinoids were observed at doses (on a mg/m^2 basis) which ranged from 0.4 to 30-fold the maximum clinical dose for adults. However, a no-effect dose level was not determined in female rats. A similar effect was not observed in a 78-week mouse carcinogenicity study with omeprazole. These gastric effects in the rat are believed to be the result of sustained, pronounced hypergastrinaemia secondary to reduced production of gastric acid. Similar effects are elicited by other proton pump inhibitors, H_2-receptor antagonists and by partial fundectomy.

Genotoxicity

Esomeprazole was negative in a bacterial gene mutation assay. In clastogenicity tests, esomeprazole was positive (as was omeprazole) in an *in vitro* chromosome aberration test in human lymphocytes. However, two *in vivo* tests (a mouse micronucleus test and an *in vivo* chromosome aberration test in rat bone marrow) in the presence of long and high systemic exposure to esomeprazole, showed that esomeprazole was not clastogenic under in vivo conditions. Exposure levels in man are well below those at which clastogenic effects occurred *in vitro*.

Effects on fertility

A fertility study has not been conducted on esomeprazole. However, there was no evidence that omeprazole impaired fertility in the rat at an estimated exposure (plasma AUC) of 1-2.5 times the maximum clinical exposure for adults.

Use in pregnancy – Category B3

For esomeprazole limited clinical data on exposed pregnancies are available. NEXIUM 24HR should only be given to pregnant women if its use is considered essential.

Esomeprazole was not teratogenic in rats or rabbits at oral doses up to 800 and 250 µmol/kg.day, respectively [corresponding to respective exposures (plasma AUC) of about 6-10 times and 0.04 times the anticipated clinical value in adults]. However, in rabbits, esomeprazole was associated with reduced fetal weights and an increased incidence of minor skeletal anomalies, although these effects were most probably related to the maternal toxicity of esomeprazole in this species. No effects on the fetuses were observed in the rat teratology study, in which an adequate systemic exposure to esomeprazole was achieved.

Use in lactation

It is not known if esomeprazole or its metabolites appear in human breast milk. No studies in lactating women have been performed. Therefore NEXIUM 24HR should not be used during breast feeding

Effects on ability to drive and operate machinery

Esomeprazole is not likely to affect the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Esomeprazole is metabolised via the CYP2C19 and CYP3A4 isoforms of the hepatic cytochrome P-450 system and may be expected to interact with the pharmacokinetics of other drugs metabolised by this system.

Esomeprazole inhibits CYP2C19, the major esomeprazole metabolising enzyme. Thus, when esomeprazole is combined with drugs metabolised by CYP2C19 (see Effects of esomeprazole on other drugs), the plasma concentrations of these drugs may be increased and a dose reduction could be needed.

Other drugs that effect esomeprazole

Clarithromycin

Concomitant administration of esomeprazole and a CYP3A4 inhibitor, clarithromycin (500 mg bid), resulted in a doubling of the exposure (AUC) to esomeprazole. Dose adjustment of esomeprazole is not required.

Concomitant administration of esomeprazole and a combined inhibitor of CYP2C19 and CYP3A4, such as voriconazole, may result in more than doubling of the esomeprazole exposure. However, dose adjustment of esomeprazole, with normal dosage, is not required.

CYP3A4 is a less important pathway than CYP2C19. However, inhibitors of CYP3A4 other than clarithromycin (e.g. ketoconazole, itraconazole, erythromycin etc) may also reduce esomeprazole clearance, although this is unlikely to be of any clinical significance.

Drugs known to induce CYP2C19 or CYP3A4 or both (such as rifampicin and St. John's wort) may lead to decreased esomeprazole serum levels by increasing the esomeprazole metabolism.

Effects of esomeprazole on other drugs

Cisapride

In healthy volunteers, concomitant administration of esomeprazole 40 mg resulted in a 32% increase in area under the plasma concentration-time curve (AUC) and a 31% prolongation of elimination half-life ($t_{½}$) but no significant increase in peak plasma levels of cisapride. The slightly prolonged QTc interval observed after administration of cisapride alone, was not further prolonged when cisapride was given in combination with esomeprazole (see PRECAUTIONS).

Cilostazol

Omeprazole as well as esomeprazole act as inhibitors of CYP2C19. Omeprazole, given in doses of 40 mg to healthy subjects in a cross-over study, increased C_{max} and AUC for cilostazol by 18% and 26% respectively, and one of its active metabolites by 29% and 69% respectively. (See CONTRAINDICATIONS).

Citalopram, clomipramine and imipramine

Because the plasma concentrations of these drugs may be increased by the concomitant administration of esomeprazole a dose reduction could be needed.

Clopidogrel

Results from studies in healthy subjects have shown a pharmacokinetic/ pharmacodynamic interaction between clopidogrel (300 mg loading dose/75 mg daily maintenance dose) and esomeprazole (40 mg p.o. daily) resulting in decreased exposure to the active metabolite of clopidogrel by an average of 40% and resulting in decreased maximum inhibition of (ADP induced) platelet aggregation by an average of 14%. Based on these data concomitant use of esomeprazole and clopidogrel should be avoided.

When clopidogrel was given together with a fixed dose combination of esomeprazole 20 mg + ASA 81 mg compared to clopidogrel alone in a study in healthy subjects there was a decreased exposure by almost 40% of the active metabolite of clopidogrel. However, the maximum levels of inhibition of (ADP induced) platelet aggregation in these subjects were similar in the clopidogrel and the clopidogrel+the combined (esomeprazole + ASA) product groups.

There are both observational and clinical studies on the clinical implications of a PK/PD interaction (with proton pump inhibitors, including omeprazole) investigating the number of major cardiovascular events when clopidogrel and proton pump inhibitors are given concomitantly.

Diazepam

Concomitant administration of 30 mg esomeprazole to healthy volunteers resulted in 45% decrease in clearance of the CYP2C19 substrate diazepam. This interaction is unlikely to be of clinical relevance.

NSAID drugs

Studies evaluating concomitant administration of esomeprazole and either naproxen (non-selective NSAID) or rofecoxib (COX-2 selective NSAID) did not identify any clinically relevant interactions in young healthy Caucasian volunteers.

Phenytoin

Concomitant administration of 40 mg esomeprazole resulted in a 13% increase in trough plasma levels of phenytoin in epileptic patients. Dose adjustment was not required in this study. It is recommended to monitor the plasma concentrations of phenytoin when treatment with esomeprazole is introduced or withdrawn.

Warfarin

Concomitant administration of 40 mg esomeprazole to warfarin-treated patients showed that, despite a slight elevation in the trough plasma concentration of the less potent R-isomer of warfarin, the coagulation times were within the accepted range. However, from post-marketing use cases of elevated INR of clinical significance have been reported during concomitant treatment with warfarin. Close monitoring is recommended when initiating and ending treatment with warfarin or other coumarin derivatives.

Tacrolimus

Concomitant administration of esomeprazole has been reported to increase the serum levels of tacrolimus.

Methotrexate

When given together with proton pump inhibitors, methotrexate levels have been reported to increase in some patients. In high-dose methotrexate administration a temporary withdrawal of esomeprazole may need to be considered.

Antiretroviral drugs

Concomitant administration with esomeprazole and atazanavir is contraindicated.

Omeprazole has been reported to interact with some antiretroviral drugs. The clinical importance and the mechanisms behind these reported interactions are not always known. Increased gastric pH during omeprazole treatment may change the absorption of the antiretroviral drug. Other possible interaction mechanisms are via CYP 2C19. For some antiretroviral drugs, such as atazanavir, decreased serum levels have been reported when given together with omeprazole and concomitant administration is not recommended. For other antiretroviral drugs, such as saquinavir, increased serum levels have been reported. There are also some antiretroviral drugs for which unchanged serum levels have been reported when given with omeprazole. Due to the similar pharmacodynamic effects and pharmacokinetic properties of omeprazole and esomeprazole, concomitant administration with esomeprazole and antiretroviral drugs is not recommended.

Medicinal products with pH dependent absorption

The decreased intragastric acidity during treatment with esomeprazole and other PPIs, might increase or decrease the absorption of drugs if the mechanism of absorption is influenced by gastric acidity. In common with the use of other inhibitors of acid secretion or antacids, the absorption of drugs such as ketoconazole, itraconazole and erlotinib can decrease and the absorption of drugs such as digoxin can increase during treatment with esomeprazole. Concomitant treatment with omeprazole (20 mg daily) and digoxin in healthy subjects increased the bioavailability of digoxin by 10% (up to 30% in two out of ten subjects).

Potential interactions that have been excluded

Amoxycillin or quinidine

Esomeprazole has been shown to have no clinically relevant effects on the pharmacokinetics of amoxicillin or quinidine.

Effect on laboratory tests

Chromogranin A (CgA) increases due to decreased gastric acidity. The increased CgA level may interfere with investigations for neuroendocrine tumours. To avoid this interference the esomeprazole treatment should be temporarily stopped 5 to 14 days before CgA measurement and that measurements should be repeated if levels have not normalised by this time.

ADVERSE EFFECTS

NEXIUM 24HR is well tolerated.

Clinical trials and post-marketing data

The following adverse reactions have been identified or suspected in the clinical trials programme and/or from post-marketing experience for esomeprazole. None was found to be dose-related.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Blood and lymphatic system disorders

Rare: leukopenia, thrombocytopenia
Very rare: agranulocytosis, pancytopenia

Immune system disorders

Rare: hypersensitivity reactions e.g. angioedema and anaphylactic reaction/shock

Metabolism and nutrition disorders

Uncommon: peripheral oedema
Rare: hyponatraemia
Very rare: hypomagnesaemia; severe hypomagnesaemia may result in hypocalcaemia. Hypomagnesaemia may also result in hypokalaemia

Psychiatric disorders

Uncommon: insomnia
Rare: agitation, confusion, depression
Very rare: aggression, hallucination

Nervous system disorders

Common: headache
Uncommon: dizziness, paraesthesia, somnolence
Rare: taste disturbance

Eye disturbances

Rare: blurred vision

Ear and labyrinth disorders

Uncommon: vertigo

Respiratory, thoracic mediastinal disorders

Rare: bronchospasm

Gastrointestinal

Common: abdominal pain, diarrhoea, flatulence, nausea/vomiting, constipation
Uncommon: dry mouth
Rare: stomatitis, gastrointestinal candidiasis
Very rare: microscopic colitis

Hepatobiliary disorders

Uncommon: increased liver enzymes
Rare: Hepatitis with or without jaundice
Very rare: hepatic failure, hepatic encephalopathy

Skin and subcutaneous tissue disorders

Uncommon: dermatitis, pruritus, urticaria, rash
Rare: alopecia, photosensitivity
Very rare: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN)

Muskuloskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia
Very rare: muscular weakness

Renal and urinary disorders

Very rare: Interstitial nephritis

Reproductive system and breast disorders

Very rare: gynaecomastia

General disorders and administration site conditions

Rare: malaise, hyperhidrosis

DOSAGE AND ADMINISTRATION

Tablets

NEXIUM 24HR tablets should be swallowed whole with liquid. The tablets should not be chewed or crushed

If required, the tablets can also be dispersed in half a glass of non-carbonated water (mineral water is not suitable). No other liquids should be used. Stir until the tablets disintegrate and drink the liquid with the pellets immediately or within 30 minutes. Rinse the glass with half a glass of water and drink. The pellets must not be chewed or crushed.

Adults

For symptomatic treatment of gastro-oesophageal reflux disease (GORD), take 1 tablet (20mg) once daily for at least 7 days, and up to 14 days. Patients should be referred to their doctor if symptoms persists or worsens while taking this course, or if symptoms persist or recur within two weeks of completing the course.

Children below the age of 18 years:

NEXIUM 24HR is not intended for use in children under the age of 18.

Geriatrics

Dose adjustment is not required in the elderly.

Hepatic insufficiency

Dose adjustment is not required in patients with mild to moderate liver impairment (Child Pugh A and B). For patients with severe liver impairment (Child Pugh C), a maximum dose of 20 mg NEXIUM 24HR should not be exceeded (see PRECAUTIONS).

Renal insufficiency

Dosage adjustment is not required in patients with impaired renal function. Due to limited experience in patients with severe renal insufficiency such patients should be treated with caution.

OVERDOSAGE

The symptoms described in connection with deliberate esomeprazole overdose are transient. The symptoms described in connection with 280 mg were gastrointestinal symptoms and weakness. Single doses of 80 mg esomeprazole were uneventful. No specific antidote is known. Esomeprazole is extensively protein bound and is therefore not readily dialyzable. As in any case of overdose, treatment should be symptomatic and general supportive measures should be utilised.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

NEXIUM 24HR tablets should be stored below 25°C.

Nexium 24HR 20 mg tablet: light pink, oblong, biconvex, film-coated tablet engraved 20 mg on one side and A/EH on the other side. Each tablet contains esomeprazole magnesium trihydrate 22.3 mg as enteric-coated pellets.

Nexium 24HR tablets are available in pack sizes of 7 and 14 tablets.

NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Limited
38-42 Wharf Road
WEST RYDE, NSW 2114

POISON SCHEDULE OF THE MEDICINE

S3 – Pharmacist Only Medicine when indicated for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days supply.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG): TBA

DATE OF MOST RECENT AMENDMENT: TBA

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® Reg TM auth user

Attachment 2





Emboss -
Full size file on Emboss layer*
* There are two levels of Embossing.

a 4/106 grose street, parramatta nsw 2150
p 02 9630 1733 f 02 9630 1930
e info@dbgraphics.com.au
w www.dbgraphics.com.au

Name:	69210 Nexium Australia 7s carton new
DBG Job No:	69210 Previous DBG Job No: 67569
Item Code:	
Date:	27/11/2014
Proof No.:	10
Dimensions:	75.0 x 115.0 x 22.0mm (Flat dimensions 179.0 x 204.3mm)
Colours:	

PROCESS CYAN* | PANTONE Rhodamine Red C | PROCESS YELLOW | PROCESS BLACK | PANTONE 2607 C | GLOSS VARNISH | Emboss | Emboss 2nd Level

Printer MUST use Pantone Rhodamine Red C in place of all Process Magenta.
***Printer MAY also use Pantone Process Blue C in place of all Process Cyan to match standard.**

PLEASE EXAMINE THIS PROOF CAREFULLY

Whilst all care and attention is taken when preparing your design, it is requested you check all details carefully. It is the responsibility of the client to ensure that all details shown are correct and ready for production. The client is responsible for any errors in the design, which are not corrected by the client, before the design is completed.
This is a proof, the colours and screen densities used in the proofing process provide a representation only, the final colour(s) may vary from this proof.

BATCH PREFIX, BATCH NUMBER, EXPIRY PREFIX AND EXPIRY DATE WILL BE PRINTED ON LINE IN COMPLIANCE WITH THE CURRENT REQUIREMENTS OF TGO69





Emboss -
Full size file on Emboss layer*
* There are two levels of Embossing.

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e info@dbgraphics.com.au
w www.dbgraphics.com.au

Name:	69210 Nexium Australia 14s carton new
DBG Job No:	69210 Previous DBG Job No: 67569
Item Code:	
Date:	21/11/2014
Proof No.:	9
Dimensions:	75.0 x 115.0 x 22.0mm (Flat dimensions 179.0 x 204.3mm)
Colours:	

PROCESS CYAN* | PANTONE Rhodamine Red C | PROCESS YELLOW | PROCESS BLACK | PANTONE 2607 C | GLOSS VARNISH | Emboss | Emboss 2nd Level

Printer MUST use Pantone Rhodamine Red C in place of all Process Magenta.
***Printer MAY also use Pantone Process Blue C in place of all Process Cyan to match standard.**

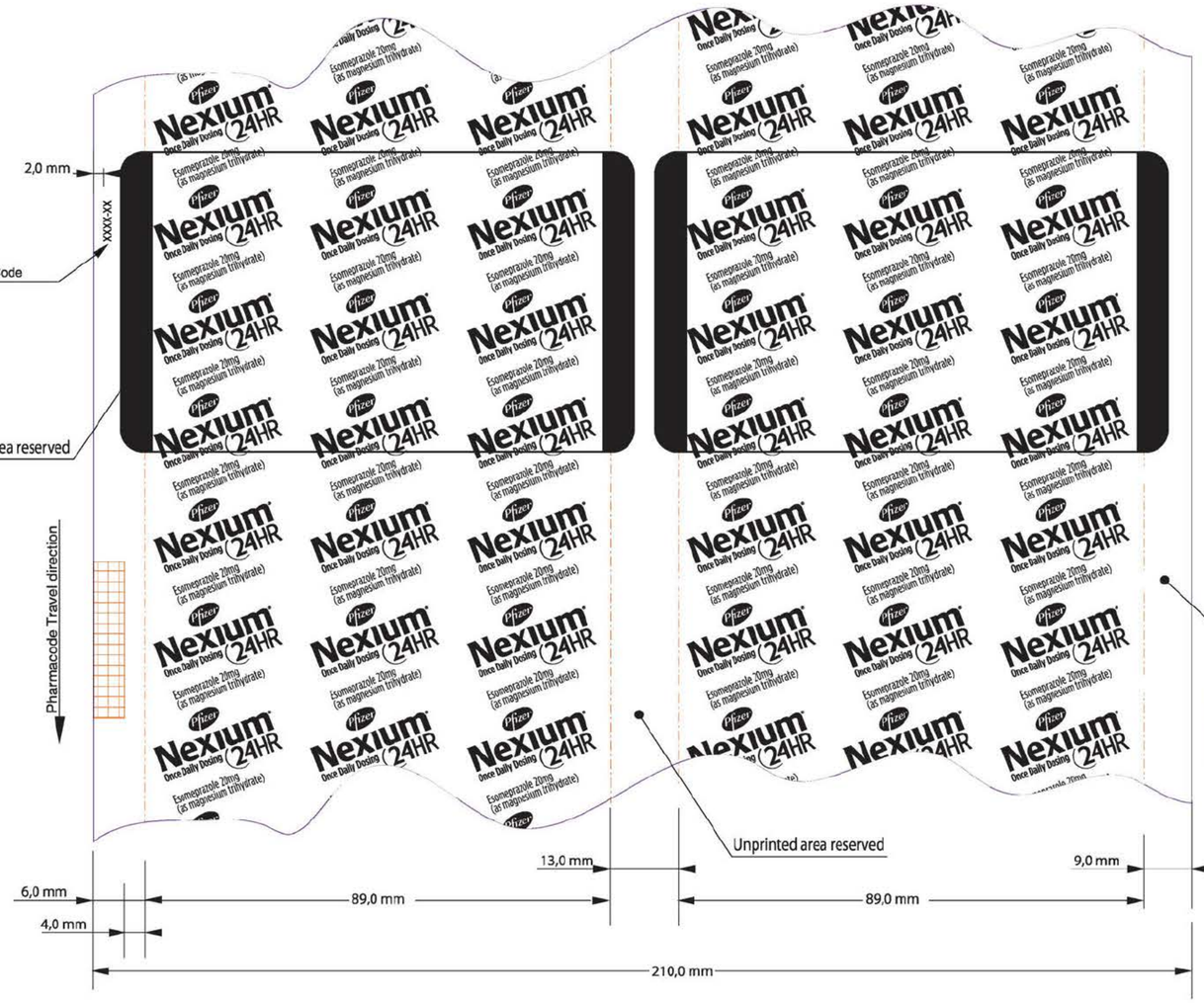
PLEASE EXAMINE THIS PROOF CAREFULLY

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BATCH PREFIX, BATCH NUMBER, EXPIRY PREFIX AND EXPIRY DATE WILL BE PRINTED ON LINE IN COMPLIANCE WITH THE CURRENT REQUIREMENTS OF TGO69

FOR NEW ARTWORKS

BATCH PREFIX, BATCH NUMBER, EXPIRY PREFIX AND EXPIRY DATE WILL BE PRINTED ON LINE IN COMPLIANCE WITH THE CURRENT REQUIREMENTS OF TGO69



Unrolling direction

a 4/106 grose street, parramatta nsw 2150
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e info@dbgraphics.com.au
w www.dbgraphics.com.au

Name:	69210 Nexium blister
DBG Job No:	69210
Item Code:	
Date:	30/10/2014
Proof No.:	2
Dimensions:	
Colours:	

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Scale 1:1

cm 0 1 2 3 4 5

Pharma code area reserved

Text Area

CUT LINE

Ver.	Date	Reason for revision	Compiler	Revisor	PPU check	Note	Tecnical info	
01	22 May 2014	New Drawing	s.22			Insert the strips for dual codify area.	*Scale:* 1:1 Web width 210 mm (Nexium AUS)	DTP ARTWORK APRILIA PLANT
							Description **Laminate**	Drawing no. **WYA0287**

NEXIUM® 24HR Once Daily Dosing

Esomeprazole magnesium trihydrate

Consumer Medicine Information

What is in this leaflet

This leaflet answers some of the common questions people ask about **Nexium 24HR** Once Daily Dosing (referred as Nexium 24HR elsewhere in this leaflet). It does not contain all the information that is known about **Nexium 24HR**.

It does not take the place of talking to your pharmacist or doctor.

All medicines have risks and benefits. Your pharmacist or doctor will have weighed the risks of you taking Nexium 24HR against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your pharmacist or doctor.

Keep this leaflet with the medicine. You may need to read it again.

What Nexium 24HR is used for

Nexium 24HR is used for lasting symptomatic relief of frequent heartburn and stomach acid complaints due to gastro-oesophageal reflux

. This can be caused by "washing back" (reflux) of food and acid from the stomach into the food pipe (oesophagus).

Reflux can cause a burning sensation in the chest rising up to the throat, also known as heartburn.

Frequent heartburn is when you have heartburn for two or more times a week. Heartburn that occurs frequently is a typical symptom of gastro-oesophageal reflux disease (GORD).

Who Should Use Nexium 24HR

Nexium 24HR is recommended for adults over 18 years of age suffering from heartburn for two or more times a week. **Nexium 24HR** is not the right medicine for you if you suffer heartburn only occasionally (one episode of heartburn a week or less), or if you want immediate relief of heartburn.

How Nexium 24HR works

Nexium 24HR is a type of medicine called a proton-pump inhibitor (PPI). It works by decreasing the amount of acid made by the stomach, to give relief of symptoms and allows healing to take place. This does not stop food being digested in the normal way.

Nexium 24HR will start to suppress acid within a few hours, however it will not give instant symptom relief. You may need to take **Nexium 24HR** for a few days before experiencing the full effect.

Nexium 24HR is available only from your pharmacist.

There is no evidence that **Nexium 24HR** is addictive.

Before you take Nexium 24 HR

When you must not take it

Do not take Nexium 24HR if you have allergies to:

- esomeprazole or any ingredient listed at the end of this leaflet.
- any medicines containing a proton-pump inhibitor.

Some of the symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin.

Do not take Nexium 24HR if you are also taking atazanavir or cilostazol.

Please check with your pharmacist or doctor if you are taking these medicines. These medicines will be affected by **Nexium 24HR**.

Nexium 24HR is not approved for use in children and adolescents under 18 years of age.

Nexium 24HR is not intended for use in children under the age of 18.

Do not take Nexium 24HR after the use by (expiry) date printed on the pack or if the packaging is torn or shows signs of tampering.

If it has expired or is damaged, return it to your pharmacist for disposal.

If you are not sure whether you should start taking **Nexium 24HR** alone or **Nexium 24HR** in combination with any other medications talk to your pharmacist or doctor.

Before you start to take it

You must tell your pharmacist or doctor if you:

- have allergies to any other medicines, foods, dyes or preservatives
- have or have ever had any problems with your liver

- have or have ever had severe kidney problems
- have anaemia, previous gastric ulcer or gastrointestinal surgery, difficulty swallowing, persistent vomiting or vomiting of blood, blood in the stools, unexplained weight loss or some other significant medical condition
- have any other medical conditions
- have previously taken heartburn / indigestion medications continuously for 4 or more weeks to control your heartburn
- you are pregnant or plan to become pregnant

Do not take Nexium 24HR if you are pregnant or breastfeeding unless your doctor says so. Ask your doctor about the risks and benefits involved.

It is not known if it is safe for you to take Nexium 24HR while you are pregnant. It may affect your baby.

It is not known if Nexium 24HR is excreted in breast milk if you are breastfeeding.

Taking other medicines

Do not take Nexium 24HR if you are taking the following medicines:

- atazanavir - medicine used to treat viral infections such as HIV
- cilostazol - a medicine used to treat pain and/or cramping in the lower leg (or arms) due to inadequate blood flow to the muscles

Tell your pharmacist or doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop.

Some medicines may interfere with Nexium 24HR. These include:

- ketoconazole, itraconazole and voriconazole - medicines used to treat fungal infections
- diazepam - a medicine used to treat anxiety and some other conditions
- phenytoin - a medicine used to treat epilepsy or fits
- citalopram, clomipramine and imipramine - medicines used to treat depression
- St John's wort - a herbal remedy used to treat mood disorders
- clarithromycin and rifampicin - medicines used to treat bacterial infections
- warfarin or clopidogrel - medicines used to prevent blood clots
- digoxin - a medicine used to treat heart conditions
- methotrexate - a medicine used to treat arthritis and some types of cancer
- tacrolimus - a medicine used in organ transplants
- erlotinib or related medicines used to treat cancer.

These medicines may be affected by **Nexium 24HR** or may affect how well it works. You may need different amounts of your medicine or you may need to take different medicines. Your pharmacist or doctor can tell you what to do if you are taking any other medicines.

Your pharmacist or doctor has more information on medicines to be careful with or avoid while taking **Nexium 24HR**.

If you have not told your pharmacist or doctor about any of these things, tell them before you take Nexium 24HR.

How to take Nexium 24HR

Follow all directions given to you by your pharmacist or doctor carefully. These instructions may differ from the information contained in this leaflet

If you do not understand the directions on the label, ask your pharmacist or doctor for help.

How to take it and how much

Take one Nexium 24HR tablet each day,.

Swallow Nexium 24HR tablets whole with a glass of water. Do not crush or chew the tablets. If the tablets are chewed or crushed they will not work properly.

If you have difficulty swallowing the tablets:

1. Place the tablet in half a glass of non-carbonated water. Mineral water or other liquids are not suitable
2. Gently mix the tablet and water by stirring, taking care not to crush the tablet
3. Stir until the tablet dissolves into little pellets
4. Drink the liquid with the pellets immediately, or within 30 minutes. Do not chew the pellets
5. Rinse the glass with half a glass of water and drink.

Nexium 24HR can be taken with food or on an empty stomach.

When to take it

Take Nexium 24HR at about the same time each day.

Keeping a regular time for taking Nexium will help to remind you to take it.

How long to take it for

Nexium 24HR should be taken for at least 7 days and up to 14 days.

You should not take it for more than 14 days unless directed by your doctor.

If you forget to take it

If you forget to take a dose, take it as soon as you remember, and then go back to taking it as you would normally.

If it is almost time for your next dose, skip the dose you missed and take your next dose when you are meant to.

Do not take a double dose to make up for the dose that you missed.

If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

Taking too much (overdose)

Telephone your pharmacist or doctor or the Poisons Information Centre (13 11 26) or go to Accident and Emergency at your nearest hospital immediately if you think that you or anyone else may have taken too many Nexium 24HR. Do this even if there are no signs of discomfort or poisoning.

While you are taking NEXIUM 24HR

Things you must do

If you are about to be started on any new medicine, tell your doctor, dentist or pharmacist that you are taking Nexium 24HR.

Tell all doctors, dentists and pharmacists who are treating you that you are taking Nexium 24HR.

Tell your pharmacist or doctor if you become pregnant while you are taking Nexium 24HR.

Tell your pharmacist or doctor if you do not feel better while taking Nexium 24HR. If symptoms persist or recur within 2 weeks of completing the course, consult a doctor. Further examination may be required.

If you need to have any medical tests while you are taking Nexium 24HR, tell your pharmacist or doctor. It may affect the results of some tests.

Things you must not do

Do not take it to treat any other complaints unless your pharmacist or doctor tells you to.

Do not give this medicine to anyone else, even if their symptoms seem similar to yours.

Side effects

Tell your pharmacist or doctor as soon as possible if you do not feel well while you are taking Nexium 24HR.

All medicines can have side effects. Sometimes they are serious, most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your pharmacist or doctor to answer any questions you may have.

Tell your pharmacist or doctor if you notice any of the following and they worry you:

- nausea or vomiting
- constipation
- diarrhoea
- headache
- wind
- stomach pain
- skin rash, itchy skin
- dizziness
- dry mouth.

These side effects are usually mild.

Tell your pharmacist or doctor immediately if you notice any of the following:

- blurred vision
- mood changes, confusion or depression
- muscle pain or weakness, joint pain
- increase in breast size (males)
- increased sweating
- changes in sleep patterns
- fever
- increased bruising
- "pins and needles"
- hair loss
- tremor
- blood in the urine

These side effects may require medical attention.

If you notice any of the following happen, tell your pharmacist or doctor immediately or go to Accident and Emergency at the nearest hospital:

- shortness of breath, wheezing or difficulty breathing
- swelling of the face, lips, tongue or other parts of the body
- severe skin reaction which may include rash, itching, redness, blistering or peeling of the skin
- signs of liver inflammation including yellowing of the skin or eyes, feeling generally unwell, nausea, vomiting, loss of appetite.

These are very serious side effects. You may need urgent medical treatment or hospitalisation. Occasionally, **Nexium 24HR** may be associated with changes in your liver or blood, which may require your doctor to do certain blood tests.

Tell your pharmacist or doctor if you think you have any of these effects or notice anything else that is making you feel unwell.

Some people may get other side effects while taking **Nexium 24HR**.

Other problems are more likely to arise from the condition itself rather than the treatment.

For this reason, contact your doctor immediately if you notice any of the following:

- pain or indigestion during treatment with **Nexium 24HR**
- you begin to vomit blood or food
- you pass black (blood-stained) motions.

After taking it

Storage

Keep your Nexium 24HR in the blister pack until it is time to take them.

If you take **Nexium 24HR** out of the blister pack it will not keep well.

Keep it in a cool, dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom or near a sink.

Do not leave it in the car or on a window sill.

Heat and dampness can destroy some medicines.

Keep it where young children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your pharmacist or doctor tells you to stop taking Nexium 24HR or the tablets have passed their expiry date, ask your pharmacist what to do with any tablets you have left over.

Product description

What Nexium 24HR looks like

Nexium 24HR 20 mg are light pink, oblong shaped tablets engraved 20 mg on one side and A / EH on the other.

Ingredients

Each **Nexium 24HR** tablet contains esomeprazole magnesium trihydrate as the active ingredient equivalent to esomeprazole 20mg

Plus the following inactive ingredients,

- Glyceryl monostearate (E 471)
- Hydroxypropyl cellulose
- Hypromellose
- Magnesium stearate (E 572)
- Methacrylic acid copolymer
- Microcrystalline cellulose (E 460).
- Paraffin synthetic
- Macrogol 6000
- Polysorbate 80 (E 433)
- Crospovidone
- Sodium stearyl fumarate
- Purified talc (E 553(b))
- Titanium dioxide (E 171)
- Triethyl citrate
- Sugar spheres (maize starch and sucrose).

The tablets are coloured with iron oxide red CI77491 and iron oxide yellow CI77492

Nexium 24HR tablets do not contain gluten.

Nexium 24HR tablets are available in blister packs of 7 or 14 tablets.

Sponsor

Pfizer Australia Pty Limited

38-42 Wharf Rd,

West Ryde NSW 2114

This leaflet was prepared March 2014.

Australian Registration Number

Nexium 24HR Once Daily Dosing: AUST R XXXXXX

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