s47F

From: s22
Sent: Wednesday, 17 April 2024 5:52 PM
To: s22
Cc: OTC Medicines
Subject: OM-2023-00902-1 & OM-2024-00299-1 s25 approvals [SEC=UNOFFICIAL]
Attachments: OM-2024-00299-1 - s25 - approval.pdf; OM-2023-00902-1 - s25 - approval.pdf

Dear s22

Please find the approval letters for these applications attached.

Regards
s22

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Submission No.: OM-2024-00299-1

s22 [redacted]

The Managing Director
Aspen Pharmacare Australia Pty Ltd
s22 [redacted]

s22 [redacted]

Dear Sir/Madam

APPLICATION UNDER s. 23 TO REGISTER A NEW MEDICINE UNDER s. 25 IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

I refer to your application under section 23 of the *Therapeutic Goods Act 1989* (the Act) dated 10 April 2024 to register

ZANTAC ranitidine 150mg (as hydrochloride) tablets

(the medicine) in the Australian Register of Therapeutic Goods (the ARTG).

Decision

As delegate of the Secretary of the Department of Health and Aged Care, I am:

- under subsection 25(3) of the Act, approving the registration of the medicine in the ARTG,
- under subsection 25AB(2) of the Act, notifying you of the decision to register the medicine,
- under subsections 25AA(1) of the Act, approving the text of the PI for the medicine**,**
- under paragraph 25AB(3)(b) of the Act, notifying you of the approved PI as set out in **Attachment 2**,
- under subsection 28(2B) of the Act, applying conditions of registration of the medicine, as outlined under '**Conditions of Registration**' below.

This approval is based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application.

The approved indication for the medicine is:

Effective long lasting relief from heartburn and acid indigestion.

Section 25, subsections 25AA(1) and (1A), section 25AB and section 28 of the Act can be found online at the following link: https://www.legislation.gov.au/Series/C2004A03952

Date of effect and supply

The date of effect of the new registration is the date specified in the Certificate of Registration, a copy of which may be obtained via the Business Services (eBS) facilities shortly after receipt of the patent certification requested below. This should be the date included under the heading "date of the most recent amendment" at the end of approved PI as set out at **Attachment 2.** Please update the PI with the date of effect in the certificate of Registration.

Supply of the approved medicine is not permitted until it is registered in the ARTG.

Conditions of registration

The conditions applying to the new registration of the medicine are:

1. Conditions applicable to all therapeutic goods as specified in the current edition of the document "Conditions- standard and specific: Applying to registered or listed therapeutic goods under section 28 of the *Therapeutic Goods Act 1989*", and
2. Conditions applicable to the relevant category and class of therapeutic goods as specified in the current edition of the document " Conditions- standard and specific: Applying to registered or listed therapeutic goods under section 28 of the *Therapeutic Goods Act 1989*", and
3. The following specific condition:

    a. The goods must conform with the finished product specification as described in **Attachment 3**. All tests specified in the finished product release specification must be performed prior to release on all batches of the product unless otherwise agreed by the TGA and indicated on the attached finished product specification. Testing on a rotational basis or some other form of reduced testing, or changes to the finished product specification, may only occur following submission of a 'variation' application and approval by the TGA.

Action required of you

Before the medicine can be included in the ARTG, you are required to either:

- notify the Secretary using the approved form that the patent certification under subsection 26B(1) of the Act is not required in relation to the application; or
- provide a certificate required under subsection 26B(1) of the Act.

Note:

The requirement for patent certificates does not apply to applicants for registration of medicines who are not required to submit evidence or information to establish the safety or efficacy of the goods as part of the registration process. In these circumstances, the applicants are only required to notify the Secretary in the approved form that the subsection 26B(1) patent certificate is not required in relation to the application.

The notification form and patent certificate can be downloaded via the TGA website (http://www.tga.gov.au/form/australia-united-states-free-trade-agreement). You should forward the completed and signed certificate or notification to otc.medicines@health.gov.au. A certificate of registration can only be issued after receipt of the completed and signed certificate or notification.

Review rights

Details of your review rights are at **Attachment 1**.

Your obligations in relation to Product Information

You are reminded that an approved PI for a medicine cannot be changed without the approval of the Secretary under subsection 25AA(4) of the Act.

You are also reminded that the CMI must comply with the requirements set out in the Therapeutic Goods Regulations 1990 which includes the obligation to ensure the CMI that must be supplied with the medicine is 'consistent with' the approved PI.

Other Matters

Copies of the final medicine labels are provided at **Attachment 4**. Please note that your product labels have not been evaluated for compliance with State and Territory labelling requirements.

A copy of the final consumer medicine information is provided at **Attachment 5**.

You are reminded of the pharmacovigilance reporting requirements as set out in the document "*Pharmacovigilance responsibilities of medicine sponsors – Australian recommendations and requirements*", including the requirement to keep the Australian pharmacovigilance contact person details up to date through the TGA Business Services electronic portal.

Please note that it is your responsibility to ensure that current Good Manufacturing Practice clearance letters are maintained for all overseas sites of manufacture registered for the products.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully

Signed and authorised by
s22
Delegate of the Secretary
Complementary & OTC Medicines Branch
s22

17 April 2024

Attachments:

1. Review rights
2. Product information
3. Finished product specification
4. Labels
5. Consumer medicine information

Attachment 1

Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: '**decision.review@health.gov.au**'

Subject: "**<insert name of person/company making request>** - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989*"

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "… - Email 1 of 3", "… - Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of the Act, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome

of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.
Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.
NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

Attachment 2 – Product information

AUSTRALIAN PRODUCT INFORMATION

ZANTAC ranitidine (as hydrochloride) tablets

1. NAME OF THE MEDICINE

Ranitidine hydrochloride.

2. and 3. QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Zantac 150 mg tablets are white film-coated round tablets engraved "150" on one face and plain on the other. The tablets contain 150 mg ranitidine (as hydrochloride).

Zantac 300 mg tablets are white capsule-shaped, film-coated tablets engraved "300" on one face and plain on the other. The tablets contain 300 mg ranitidine (as hydrochloride).

For the full list of excipients, see Section 6.1 List of excipients.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. Short-term treatment of proven duodenal ulcer and gastric ulcer for prophylaxis against recurrent haemorrhage.
2. Maintenance treatment to reduce the risk of relapse in duodenal ulcer.
3. Maintenance treatment for periods up to one year to reduce the risk of relapse in patients with documented healing of benign gastric ulcer.
4. Treatment of gastrinoma (Zollinger-Ellison syndrome).
5. Short-term symptomatic treatment of reflux oesophagitis unresponsive to conservative anti-reflux measures and simple drug therapies such as antacids.
6. Maintenance treatment to reduce the risk of relapse of reflux oesophagitis.
7. Treatment of scleroderma oesophagitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Zantac tablets are administered by mouth.

1. **Acute duodenal or gastric ulceration:**
   300 mg taken as a single dose at bedtime, or 150 mg taken twice daily, in the morning and at bedtime.

   It is not necessary to time the dose in relation to meals. In most cases healing will occur in four weeks although a small number of patients may require an additional 2-4 weeks' therapy.

   Maintenance treatment:
   Duodenal ulcer: 150 mg taken at night.

   As smoking is associated with a higher rate of ulcer relapse, patients should be advised to stop smoking. In patients unable to stop smoking, a dose of 300 mg at night provides additional therapeutic benefit.

   Gastric ulcer: 150 mg taken at night for a period of one year.

2. **Gastrinoma (Zollinger-Ellison syndrome):**
   150 mg taken 3 times daily initially and increased, as necessary, to 600-900 mg/day.

3. **Reflux oesophagitis:**
300 mg taken as a single dose at bedtime or 150 mg taken twice daily in the morning and at bedtime. It is not necessary to time the dose in relation to meals.

In severe reflux oesophagitis the efficacy of 300 mg, taken as a single dose at bedtime, has been established for up to 3 months.

Maintenance treatment:
Reflux oesophagitis: 150 mg taken twice daily in the morning and at bedtime.

4.3 CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastric ulcer
Treatment with a histamine H_2 – antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Zantac tablets is instituted.

Long-term use
The risk of ulcer recurrence is determined by many factors. In some cases, long periods of treatment may be necessary and/or repeated. Evidence from controlled clinical trials of up to 18 months continuous treatment with Zantac has not revealed any undue untoward effects.

Higher doses
The use of higher than recommended doses of intravenous H_2 - antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

Porphyria
Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Zantac should therefore be avoided in patients with a history of acute porphyria.

Gastric pH
Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

Use in renal impairment
Ranitidine is excreted via the kidney and in the presence of renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly in the presence of significant renal impairment, serum levels should be monitored and dosage adjustments made. The clearance of ranitidine is increased during haemodialysis.

Use in the elderly
In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia, A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H_2 – receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1,63 (95% CI, 1,07–2,48).

Paediatric use
Experience with ranitidine tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however, been used successfully in children aged 8–18 years in doses up to 150 mg twice daily.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system:
Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2) Competition for renal tubular secretion:
Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

3) Alteration of gastric pH:
The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

If high doses (2g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of two hours.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effects of ranitidine on human fertility. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine.

Use in pregnancy
Pregnancy category: B1. The safety of ranitidine in pregnancy has not been established. Ranitidine crosses the placenta. Zantac should only be used during pregnancy if considered essential. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus.

Use in lactation
Ranitidine is secreted in breast milk in lactating mothers, but the clinical significance of this has not been fully evaluated. Zantac should only be used by nursing mothers if considered essential.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 http://www.tga.gov.au/reporting-problems.

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has not been clear in many cases. Headache, sometimes severe, has been reported in a very small proportion of patients.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Rare cases of reversible mental confusion, depression and hallucinations have been reported, predominantly in severely ill and elderly patients. In addition, reversible involuntary movement disorders have been reported rarely. There have been a few reports of reversible blurred vision suggestive of a change in accommodation. Reversible impotence has been reported rarely.

Cardiovascular: As with other H_2 - receptor antagonists rare reports of tachycardia, bradycardia, premature ventricular beats, AV block, and asystole.

Gastrointestinal: Constipation, diarrhoea, nausea/vomiting, abdominal discomfort/pain.

Hepatic: Transient and reversible changes in liver-function tests can occur. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

Musculoskeletal: Rare reports of arthralgias and myalgia.

Haematologic: Rare reports of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplasia have been reported. Blood count changes (leucopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine, no anti-androgenic activity, and cimetidine-induced gynaecomastia and impotence in hypersecretory patients have resolved when ranitidine was substituted. However, occasional cases of breast conditions such as gynaecomastia and galactorrhoea, impotence and loss of libido have been reported in male patients receiving ranitidine but the incidence did not differ from that in the general population.

Integumental: Rash including rare cases of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

Renal: Very rare cases of acute interstitial nephritis have been reported.

Other: Rare cases of hypersensitivity reactions (eg, fever, bronchospasm, anaphylactic shock, urticaria, angioneurotic oedema, hypotension, chest pain, rash, eosinophilia), small increases in serum creatinine. Acute pancreatitis has been reported rarely.

4.9 OVERDOSE

There has been limited experience with overdosage with oral doses of ranitidine. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience. See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Animal experiments both *in vitro* and *in vivo* have established that ranitidine is a selective, competitive antagonist of histamine at H_2 - receptor sites. Ranitidine has no significant interaction at histamine H_1 - receptors, muscarinic receptors or beta-adrenoceptors. Ranitidine is a potent inhibitor of gastric secretion in the rat and dog.

All the evidence from human studies is compatible with a selective, competitive antagonism of histamine H_2 - receptors by ranitidine in man. Oral administration of ranitidine inhibits both basal gastric secretions and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. On a weight basis ranitidine is between 4 and 9 times more potent than cimetidine.

After oral administration of ranitidine, the plasma concentrations of ranitidine achieved are directly related to the dose administered. A plasma ranitidine concentration of 50-100 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%.

Inhibition of pentagastrin-induced gastric acid secretion increases with dose, being approximately 90% two hours after an oral 150 mg dose and a significant effect is still evident 12 hours after this dose. In 10 patients with duodenal ulcer, 150 mg ranitidine given orally every 12 hours significantly reduced mean 24 hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90% whereas cimetidine (200 mg three times daily and 400 mg at night) reduced mean 24 hour hydrogen ion activity by 48% and nocturnal gastric acid output by 70%.

Pepsin secretion is also inhibited by ranitidine, but secretion of gastric mucus is not affected. Ranitidine does not alter the secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancreozymin. Reduction in gastric acid secretion induced by ranitidine 150 mg twice daily for 7 days did not cause bacterial overgrowth in the stomach.

Pulse rate, blood pressure, electrocardiogram and electroencephalogram were not significantly affected in man following recommended doses of ranitidine.

Chronic ranitidine therapy (300 mg/day for 28 days) had no effect on serum prolactin, gastrin, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone, gonadotrophins, testosterone, oestriol, progesterone or cortisol levels.

One study in 30 male duodenal ulcer patients showed a significant decrease in basal thyroxine levels after 4 weeks' treatment with 300 mg ranitidine daily, but no significant change in thyroid stimulating hormone was noted.

Clinical trials
No clinical trial data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Peak plasma levels occur about 2-3 hours after oral administration of ranitidine. Absorption is not significantly altered by food or concurrent antacid administration.

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 580 ng/mL) occurred after 1 to 3 hours. Two distinct peaks or a plateau in the absorption phase suggest reabsorption of drug secreted into the intestine. The absolute bioavailability of ranitidine is 50 to 60%, and plasma concentrations increase proportionally with increasing dose up to 200 mg. Bioavailability of ranitidine is

approximately 50%. Serum protein binding of ranitidine in man is in the range 10-19%. The elimination half-life is approximately 2 hours.

Distribution
Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism
The fraction of the dose recovered as metabolites includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide and small amounts of desmethylranitidine and the furoic acid analogue. . The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% after oral administration of the drug.

Excretion
Plasma concentrations decline bi-exponentially, with a terminal half-life of 2 to 3 hours. The major route of elimination of unchanged ranitidine is renal. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Patients over 50 years of age:
In patients over 50 years of age, half life is prolonged (3 to 4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

Impairment of renal function requires a reduction in dosage (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Impairment of liver function may increase the bioavailability of ranitidine but has no significant effect on the elimination half-life, However, in the presence of normal renal function, no dosage reduction for oral or intravenous ranitidine appears necessary in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Croscarmellose sodium, magnesium stearate, microcrystalline cellulose and Opadry II white YS-22-18096.

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, keep dry. Protect from heat.

6.5 NATURE AND CONTENTS OF CONTAINER

Zantac 150 mg tablets are available in Al/Al foil blister packs of 2 (starter packs), 7, 14, 28, 60 and 90 tablets.

Zantac 300 mg tablets are available in Al/Al foil blister packs of 2 (starter packs), 7, 14, 30 tablets.

(Note: Not all strengths or pack sizes are marketed in Australia.)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

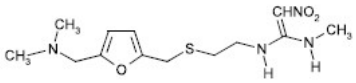
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ranitidine hydrochloride is a histamine H_2 - receptor antagonist. It is an aminoalkyl-substituted furan and is structurally different from cimetidine lacking the imidazole ring and the cyanoguanidine group. Ranitidine hydrochloride is a white to pale yellow granular solid with a melting point of about 140°C. It is freely soluble in water, with a partition co-efficient between n-octanol and water log P = 0.20. It has a slightly bitter taste and sulfurlike odour.

Molecular formula: $C_{13}H_{22}N_4O_3S.HCl$, molecular weight: 350.9, chemical name: N-(2-(((5-((Dimethylamino)methyl)-2-furan-yl)methyl)thio)ethyl)N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride.

Chemical structure:



. HCl

CAS number:
66357-59-3

7 MEDICINE SCHEDULING (POISONS STANDARD)

Prescription Only Medicine (S4):
- Zantac 150 mg tablets: 2, 6, and 60 tablets
- Zantac 300 mg tablets: 2, 4, and 30 tablets

Pharmacy Medicine (S2):
- Zantac 150 mg: 28 tablets
- Zantac 300 mg: 2 and 14 tablets

Not scheduled:
- Zantac 150 mg: 2, 4, 7 & 14 tablets
- Zantac 300 mg: 7 tablets

8 SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street

St Leonards NSW 2065
Australia

9 DATE OF FIRST APPROVAL

Zantac 150 mg tablets [AUST R 53324]: 20/11/1995
Zantac 300 mg tablets [AUST R 53323]: 20/11/1995
Zantac 150 mg (OTC) [AUST R 71786]: 8/11/1999
Zantac Double Strength 300 mg tablets [AUST R 95076]: 11/07/2003

10 DATE OF REVISION

xxxx

Summary table of changes

Section changed	Summary of new information
6.1	Excipient update
6.4	Update to storage temperature and statement
9	Addition of date of first approval of OTC tablet variants.
PI end	Deletion of redundant trademark statement.
All	Deletion of relevant PI information for specific dosage forms other than tablets.
All	General formatting and text insertions for clarity e.g. 'round' in section 2.

Attachment 3 – Finished product specification

s47 [redacted]

PRODUCT RELEASE SPECIFICATION

Product Name : Ranitidine Tablets 150 mg			
Standard	: IH	Reference	: BP/Ph.Eur/IH
Code No.	: 2005549	Specification No.	: 2005549/PRS/R4
Effective Date	: Draft Spec	Page No.	: 1 of 3
Shelf life	: 24 Months	Supersedes	: 2005549/PRS/R3
Market / Customer: Australia/Aspen Pharmacare			

REASON FOR REVISION:

Revision No.	Changes incorporated	Effective Date
R 1	New specification introduced	27-Mar-2017
R 2	Change in the assay limit from "Not less than 98.0 % and not more than 105.0 % (Not less than 147.0 mg and not more than 157.5 mg)" to "Not less than 95.0 % and not more than 105.0 % (Not less than 142.5 mg and not more than 157.5 mg)" in the In-process Specification (Lubricated granules) as per change control number: PC-PYD/2017/101	10-Apr-2017
R 3	Change in organization name as per change control number PC-CRP/2018/063. Inclusion of note under footnote in PRS and SLS. Inclusion of Related Substances by LC-HRMS (For NDMA impurity) test in PRS and SLS, Changes done as per change control number PC-TSG/2019/357.	22-Nov-2019
R4	Change in reference STP number as per SOP-GQC/052 due to introduction of STP into LIMS. Change in format as per SOP-GQC/053. Updation of storage, shelf life, market/customer name. Updation of specification limit for N-Nitrosodimethylamine (NDMA Impurity) under Related Substances by LC-HRMS test in PRS and SLS stages. Updation of specification limit for Impurity 1(Impurity H), Impurity 2 (Impurity C) , Impurity 3 (Impurity E), Impurity 4 (Impurity D), Total impurities (Not including impurity A) under Related substances by UPLC test in PRS and SLS stages. Inclusion of Impurity A under Related substances by UPLC test in PRS and SLS stages. Removal of footnote related to Related Substances by LC-HRM test from PRS and SLS stages. Changes done as per record number: 417349.	Draft

GQC/053/F-09/R1

s47 [redacted]

PRODUCT RELEASE SPECIFICATION

Product Name : Ranitidine Tablets 150 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005549	Specification No. : 2005549/PRS/R4
Effective Date : Draft Spec	Page No. : 2 of 3
Shelf life : 24 Months	Supersedes : 2005549/PRS/R3
Market / Customer: Australia/Aspen Pharmacare	

S No.	Test	Specification limits	Test method
1	Description	White film coated round tablet, embossed with '150' on one side and plain on the other side	ASD/GP/0362
2	Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	IH
3	Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	IH
4	Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	BP
5	Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	IH
6	Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	ASD/GP/0424
7	Related substances by UPLC		IH
	i) Impurity A	Not more than 0.5%	
	ii) Impurity 1 (Impurity H)	Not more than 0.2%	
	iii) Impurity 2 (Impurity C)	Not more than 0.2%	
	iv) Impurity 3 (Impurity E)	Not more than 0.2%	
	v) Impurity 4 (Impurity D)	Not more than 0.2%	
	vi) Largest single unknown impurity	Not more than 0.2%	
	vii) Total impurities (Not including impurity A)	Not more than 1.0%	
8	Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	IH
		Label claim Limit	
	Assay in %	150 mg - Not less than 98.0 % and not more than 105.0 %	
	Assay in mg	150 mg - Not less than 147.0 mg and not more than 157.5 mg	

GQC/053/F-09/R1

s47 [redacted]

PRODUCT RELEASE SPECIFICATION

Product Name : Ranitidine Tablets 150 mg			
Standard : IH		Reference : BP/Ph.Eur/IH	
Code No. : 2005549		Specification No. : 2005549/PRS/R4	
Effective Date : Draft Spec		Page No. : 3 of 3	
Shelf life : 24 Months		Supersedes : 2005549/PRS/R3	
Market / Customer: Australia/Aspen Pharmacare			
9	Microbial limits		ASD/GP/0539
	i) Total aerobic microbial count	Not more than 1000 cfu/g	
	ii) Total combined yeast & molds count	Not more than 100 cfu/g	
	iii) Escherichia coli	Absent/1 g	
10	Related Substances by LC-HRMS		IH
	i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than s47 [redacted]	

Reference STP No.: 2005549/FPSTP

STORAGE: Store below 25° C. Protect from heat.

PACKING :
Not Applicable

NOTE :
i) IH refers to In-house.
ii) Report Assay value in both Percentage and Milligram.
iii) Residual solvents : Based on the information provided by the suppliers, only Class 2 and / or Class 3 solvents are likely to be present in the ingredients used to manufacture this product. The cumulative quantity of the solvents, contributed by all the ingredients are within the limit and the manufacture process of the product does not include any solvent. Since the Residual solvents are within the limits specified in the ICH guideline Q3C (Option 1) in the Finished Product, these solvents are not tested.
iv) Microbial limits test will be performed on initial three batches and on every 10th batch manufactured or once per year, whichever falls first for monitoring purpose only (for information) and not for product release criteria.

s22 [redacted]

GQC/053/F-09/R1

s47 [redacted]

SHELF LIFE SPECIFICATION

Product Name : Ranitidine Tablets 150 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005549	Specification No. : 2005549/SLS/R4
Effective Date : Draft Spec	Page No. : 1 of 3
Shelf life : 24 Months	Supersedes : 2005549/SLS/R3
Market / Customer: Australia/Aspen Pharmacare	

REASON FOR REVISION:

Revision No.	Changes incorporated	Effective Date
R 1	New specification introduced	27-Mar-2017
R 2	Change in the assay limit from "Not less than 98.0 % and not more than 105.0 % (Not less than 147.0 mg and not more than 157.5 mg)" to "Not less than 95.0 % and not more than 105.0 % (Not less than 142.5 mg and not more than 157.5 mg)" in the In-process Specification (Lubricated granules) as per change control number: PC-PYD/2017/101	10-Apr-2017
R 3	Change in organization name as per change control number PC-CRP/2018/063. Inclusion of note under footnote in PRS and SLS. Inclusion of Related Substances by LC-HRMS (For NDMA impurity) test in PRS and SLS, Changes done as per change control number PC-TSG/2019/357.	22-Nov-2019
R4	Change in reference STP number as per SOP-GQC/052 due to introduction of STP into LIMS. Change in format as per SOP-GQC/053. Updation of storage, shelf life, market/customer name. Updation of specification limit for N-Nitrosodimethylamine (NDMA Impurity) under Related Substances by LC-HRMS test in PRS and SLS stages. Updation of specification limit for Impurity 1(Impurity H), Impurity 2 (Impurity C) , Impurity 3 (Impurity E), Impurity 4 (Impurity D), Total impurities (Not including impurity A) under Related substances by UPLC test in PRS and SLS stages. Inclusion of Impurity A under Related substances by UPLC test in PRS and SLS stages. Removal of footnote related to Related Substances by LC-HRM test from PRS and SLS stages. Changes done as per record number: 417349.	Draft

GQC/053/F-09/R1

s47 [redacted]

SHELF LIFE SPECIFICATION

Product Name : Ranitidine Tablets 150 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005549	Specification No. : 2005549/SLS/R4
Effective Date : Draft Spec	Page No. : 2 of 3
Shelf life : 24 Months	Supersedes : 2005549/SLS/R3
Market / Customer: Australia/Aspen Pharmacare	

S No.	Test	Specification limits	Test method
1	Description	White film coated round tablet, embossed with '150' on one side and plain on the other side	ASD/GP/0362
2	Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	IH
3	Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	IH
4	Related substances by UPLC		IH
	i) Impurity A	Not more than 0.5%	
	ii) Impurity 1 (Impurity H)	Not more than 0.2%	
	iii) Impurity 2 (Impurity C)	Not more than 0.2%	
	iv) Impurity 3 (Impurity E)	Not more than 0.2%	
	v) Impurity 4 (Impurity D)	Not more than 0.2%	
	vi) Largest single unknown impurity	Not more than 0.2%	
	vii) Total impurities (Not including impurity A)	Not more than 1.0%	
5	Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	IH
		Label claim Limit	
	Assay in %	150 mg - Not less than 95.0 % and not more than 105.0 %	
	Assay in mg	150 mg - Not less than 142.5 mg and not more than 157.5 mg	
6	Microbial limits		ASD/GP/0539
	i) Total aerobic microbial count	Not more than 1000 cfu/g	
	ii) Total combined yeast & molds count	Not more than 100 cfu/g	
	iii) Escherichia coli	Absent/1 g	
7	Related Substances by LC-HRMS		IH
	i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.32 ppm	

GQC/053/F-09/R1

s47 [redacted]

SHELF LIFE SPECIFICATION

Product Name : Ranitidine Tablets 150 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005549	Specification No. : 2005549/SLS/R4
Effective Date : Draft Spec	Page No. : 3 of 3
Shelf life : 24 Months	Supersedes : 2005549/SLS/R3
Market / Customer: Australia/Aspen Pharmacare	

Reference STP No.: 2005549/FPSTP

STORAGE: Store below 25° C. Protect from heat.

PACKING :
Not Applicable

NOTE :
i) IH refers to In-house.
ii) Report Assay value in both Percentage and Milligram.
iii) Microbial limits test to be performed for accelerated stability samples at initial and end of the study, for long term stability samples at initial and thereafter annually once.

s22 [redacted]

GQC/053/F-09/R1

Attachment 4 – Labels


Zantac
14 TABLETS
12 HOUR ACTIVE RELIEF FROM: HEARTBURN ACID INDIGESTION
aspen
New formulation
New tablet appearance
14 EASY TO SWALLOW TABLETS
ranitidine 150 mg (as hydrochloride)
Pharma Code
Complete panel required unvarnished for batch details print
ACTIVE INGREDIENT
Each tablet contains ranitidine 150 mg (as hydrochloride)
USE
Effective, long-lasting 12 hour relief from heartburn and acid indigestion due to gastro-oesophageal reflux with one tablet. Zantac works by controlling the production of stomach acid.
WARNINGS
Do not use if under 12 years of age unless directed to do so by your doctor.
This preparation is for relief of minor and temporary ailments and should be used strictly as directed.
Do not use, except on doctor's advice, with aspirin or other anti-inflammatory medicines or for any purpose other than specified on the pack.
If symptoms persist or recur within two weeks, or if new or additional symptoms occur, consult a doctor.
If breastfeeding or pregnant, or likely to become pregnant, consult a pharmacist or a doctor before use.
DIRECTIONS FOR USE
Adults and children over 12 years: Swallow 1 tablet whole (do not chew) with water as soon as you have symptoms, at any time day or night.
Maximum 2 tablets in 24 hours. Do not use for more than 14 days continuously.
Take one tablet at the first sign of symptoms. If symptoms return or persist for more than one hour, take another tablet. Do not take more than 2 tablets in 24 hours.
continued
OTHER INFORMATION
Store below 25°C.
Protect from heat.
Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street St Leonards
NSW 2065 Australia
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X XXXXXX XXXXXX


Zantac
28 TABLETS
12 HOUR ACTIVE RELIEF FROM: HEARTBURN ACID INDIGESTION
aspen
New formulation
New tablet appearance
28 EASY TO SWALLOW TABLETS
ranitidine 150 mg (as hydrochloride)
KEEP OUT OF REACH OF CHILDREN
PHARMACY MEDICINE
Pharma Code
Complete panel required unvarnished for batch details print
ACTIVE INGREDIENT
Each tablet contains ranitidine 150 mg (as hydrochloride)
USE
Effective, long-lasting 12 hour relief from heartburn and acid indigestion due to gastro-oesophageal reflux with one tablet. Zantac works by controlling the production of stomach acid.
WARNINGS
Do not use if under 12 years of age unless directed to do so by your doctor.
This preparation is for relief of minor and temporary ailments and should be used strictly as directed.
Do not use, except on doctor's advice, with aspirin or other anti-inflammatory medicines or for any purpose other than specified on the pack.
If symptoms persist or recur within two weeks, or if new or additional symptoms occur, consult a doctor.
If breastfeeding or pregnant, or likely to become pregnant, consult a pharmacist or a doctor before use.
DIRECTIONS FOR USE
Adults and children over 12 years: Swallow 1 tablet whole (do not chew) with water as soon as you have symptoms, at any time day or night.
Maximum 2 tablets in 24 hours. Do not use for more than 14 days continuously.
Take one tablet at the first sign of symptoms. If symptoms return or persist for more than one hour, take another tablet. Do not take more than 2 tablets in 24 hours.
continued
OTHER INFORMATION
Store below 25°C.
Protect from heat.
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34-36 Chandos Street St Leonards
NSW 2065 Australia
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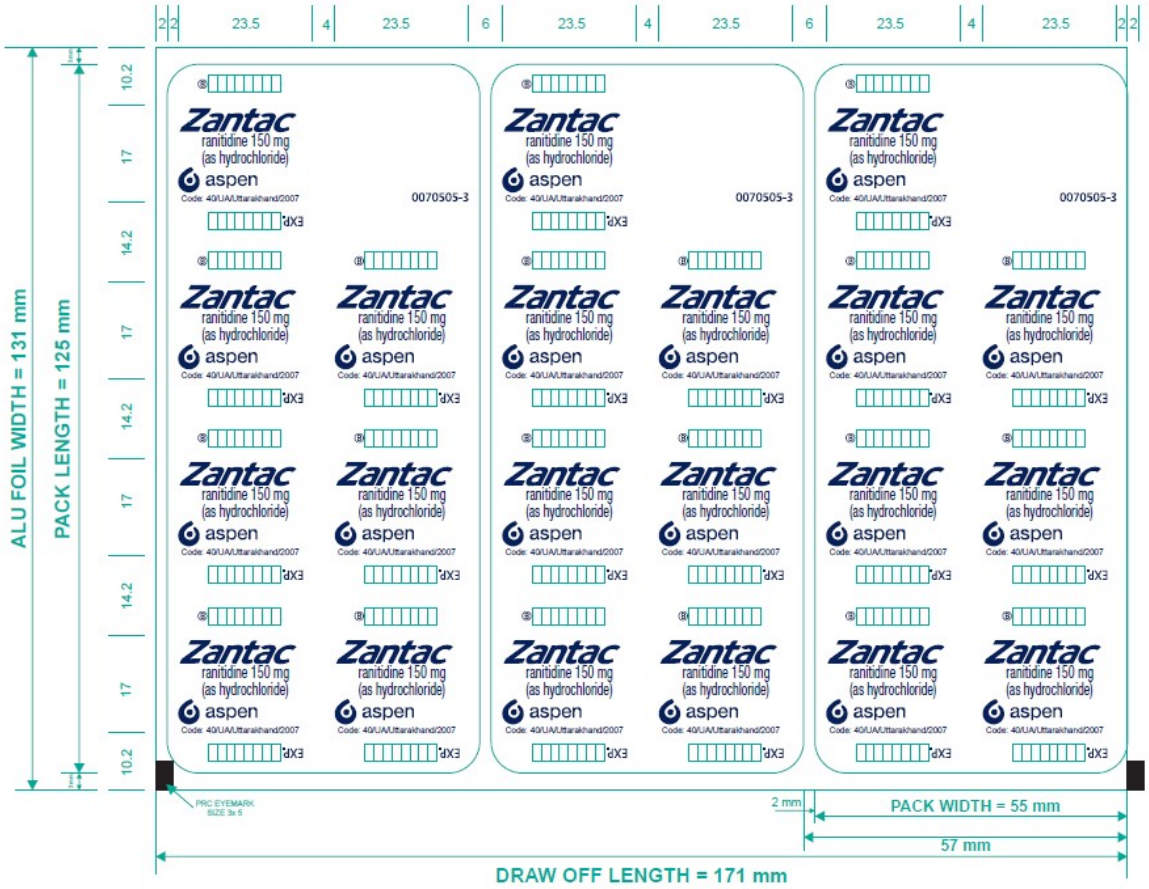

2 2 23.5 4 23.5 6 23.5 4 23.5 6 23.5 4 23.5 2 2
10.2 17 14.2 17 14.2 17 14.2 17 10.2
ALU FOIL WIDTH = 131 mm
PACK LENGTH = 125 mm
Zantac
ranitidine 150 mg
(as hydrochloride)
aspen
0070505-3
EXP
PRC EYEMARK
SIZE 3x 5
2 mm
PACK WIDTH = 55 mm
57 mm
DRAW OFF LENGTH = 171 mm

Attachment 5 – Consumer medicine information

Zantac tablets

ranitidine hydrochloride

Consumer Medicine Information (CMI)

About your Zantac tablets

Read all of this leaflet carefully before you take your medicine.

This leaflet does not have the complete information available about your medicine. If you have any questions about your medicine, you should ask your doctor or pharmacist.

All medicines have some risks. Sometimes new risks are found even when a medicine has been used for many years.

If there is anything you do not understand, ask your doctor or pharmacist. If you want more information, ask your doctor or pharmacist.

What is in my Zantac?

The medicine in your Zantac tablets is called ranitidine (as hydrochloride). This belongs to a group of medicines called H2-antagonists.

What does my Zantac do?

Zantac is mostly used to:

- treat stomach and duodenal ulcer disease (also known as peptic ulcer);
- stop these ulcers from coming back;
- treat reflux oesophagitis (also known as reflux).

These problems are caused, in part, by too much acid in the stomach. This can lead to pain such as heartburn. Zantac works by reducing the amount of acid in the stomach. This reduces the pain and also allows the ulcer and reflux to heal.

Zantac is also used to treat Zollinger-Ellison disease.

Zantac 150 mg and 300 mg tablets are either available with a doctor's prescription (for larger pack sizes) or from a pharmacist (for smaller pack sizes).

Before you take it

Do not take if:

You must not take Zantac if:

- you have ever had an allergic (hypersensitive) reaction to ranitidine or any of the ingredients listed towards the end of this leaflet.
- the expiry date (EXP) printed on the pack has passed.
- the packaging is torn or shows signs of tampering.

Tell your doctor if:

You must tell your doctor if:

- you are allergic to foods, dyes, preservatives or any other medicines
- you have ever had an allergic (hypersensitive) reaction to ranitidine or any of the ingredients listed towards the end of this leaflet.
- you are allergic to any medicine,
- you have stomach cancer,
- you have kidney disease,
- you have had stomach ulcers before and you are taking Non-Steroidal Anti-Inflammatory (NSAID) medicines.
- you have a disease known as acute porphyria.
- you are over 65 years of age.
- you have lung disease.
- you are diabetic.
- you have any problems with your immune system.
- you have to stop taking this or any other medicine for your ulcer or reflux.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, have taken any recently, or if you start new ones. This includes herbal medicines and any other medicines you have bought without a prescription.

Zantac can affect the way some other medicines work. Also other medicines can affect the way Zantac works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:

- warfarin, used to prevent blood clots
- triazolam and midazolam, used as sedatives
- ketoconazole, an anti-fungal
- atazanavir and delaviridine, used to treat HIV

- glipizide, used for diabetics.
- gefitinib, used in the treatment of cancer.
- Non-Steroidal Anti-Inflammatory (NSAID) medicines, for pain and inflammation
- procainamide or n-acetylprocainamide, used to treat heart problems
- sucralfate used to treat ulcers.

What if I am pregnant or breast feeding?

Tell your doctor if you are pregnant, likely to get pregnant or are breast feeding. Your doctor will tell you if you should take this medicine.

How do I take it

- The dosage depends on the disease that you are suffering from. Your doctor or pharmacist will usually tell you how many Zantac tablets to take and how often to take them. You will also find this information on the label of your medicine.
- The normal adult dosage is 150 to 300 milligrams per day, taken as one 150 mg tablet once or twice a day, or one 300 mg tablet at bedtime. Your doctor may prescribe a different dosage.
- Do not take extra tablets. Do not take the tablets more often than you have been told.
- It does not matter whether you take the tablets before or after food.
- Zantac tablets should be swallowed whole with a glass of water.
- Your pain or other symptoms may take a few days to go away.
- Take all the tablets your doctor has prescribed for you, even if you feel better.
- Even when you have completed your tablets, your doctor may decide to continue your treatment with Zantac, possibly at a different dosage, in order to prevent the problem coming back again.

Use in Children:

Zantac has not been studied fully in children. However, Zantac has been used with good results in children aged 8 to 18 years in doses up to 150 mg twice daily.

What should I do if I miss my dose?

If you forget to take your Zantac, take another as soon as possible unless it is nearly time for your next dose. Do not take a double dose to make up for the missed one.

Side effects

Like other medicines, Zantac may cause some side-effects. Most of the side-effects will be minor and temporary, but some may be serious. Your doctor will be able to answer any questions you may have.

Tell your doctor straight away and do not take any more Zantac if you have:

- an allergic reactions, the signs may include:
  - skin reactions such as rash (red spots), itching, skin lumps or hives
  - swelling of the eyelids, face, lips, tongue or other parts of the body
  - shortness of breath, trouble breathing, wheezing, chest pain or tightness
  - unexplained fever and feeling faint, especially when standing up.
- severe stomach pain or a change in the type of pain,
- yellow colouring of the skin or eyes (jaundice),confusion,
- general illness associated with weight loss,
- fever.
- irregular heart beat (including unusually fast or slow heart beats),
- changes to heart beat.

If you get any of the following side-effects after taking Zantac tell your doctor, but there is no immediate reason to stop taking the tablets unless you are concerned:

- headache,
- joint or muscle pains,
- dizziness,
- depression,
- constipation
- feeling sick (nausea) or vomiting
- diarrhoea
- breast tenderness and/or breast enlargement
- breast discharge.
- changes in liver function tests

If you notice any symptoms that concern you or if the tablets cause any other side-effects, tell your doctor or pharmacist.

If you have taken all the tablets and still do not feel better tell your doctor as soon as possible.

Other side effects not listed above may also occur in some people.

Overdose

In the event of an overdose you should immediately telephone your doctor or Poisons Information Centre (telephone 131126) for advice, if you think you or anyone else may have taken too much Zantac, even if there

are no signs of discomfort or poisoning. If you are not sure what to do, contact your doctor or pharmacist.

How do I store my Zantac?

- Store below 25°C, keep dry. Protect from heat.
- Keep Zantac tablets in a place where children cannot reach them.
- You will find an "expiry" (or use by) date printed on the manufacturer's label of the pack. Do not use the tablets after this date. Do not use the tablets if they are discoloured.
- Leave the tablets in the pack until you are ready to use them.

Can I let someone else use my Zantac?

Never give this medicine to someone else. The medicine is only for you. It may harm other people even if they seem to have the same symptoms that you have.

Product description

What Zantac tablets look like.

Zantac tablets come in two strengths:

150 mg - white, film coated, round tablets engraved '150' on one face and plain on the other. Available in packs of 14 tablets (from your pharmacy) or 60 tablets (from your doctor).

300 mg - white, capsule shaped, film coated tablets engraved '300' on one face and plain on the other. Available in packs of 14 tablets (from your pharmacy) or 30 tablets (from your doctor).

(Not all pack sizes are marketed.)

Ingredients

Zantac contains the active ingredient ranitidine (as ranitidine hydrochloride). Each tablet contains either 150 or 300 milligrams of ranitidine.

They also contain the inactive ingredients:

microcrystalline cellulose, magnesium stearate, croscarmellose sodium and Opadry II white YS-22-18096

Zantac tablets are free from gluten and lactose.

Who makes my Zantac?

Aspen Pharmacare Australia Pty Ltd

34-36 Chandos Street

St Leonards NSW 2065

Australia.

Australian Registration Numbers:

Zantac 150 mg tablets: AUST R 53324

Zantac 300 mg tablets: AUST R 53323

Zantac 150 mg tablets (OTC): AUST R 71786

Zantac DOUBLE STRENGTH 300 mg tablets (OTC): AUST R 95076

This leaflet was revised in February 2024.

Australian Government

Department of Health and Aged Care

Therapeutic Goods Administration

Submission ID: OM-2023-00902-1

s22 [redacted]

The Managing Director
Aspen Pharmacare Australia Pty Ltd
s22 [redacted]

s22 [redacted]

Dear Sir/Madam

APPLICATION UNDER s. 23 TO REGISTER A NEW MEDICINE UNDER s. 25 IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

I refer to your application under section 23 of the *Therapeutic Goods Act 1989* (the Act) dated 10 November 2023 to register

ZANTAC DOUBLE STRENGTH ranitidine 300mg (as hydrochloride) tablet blister pack

(the medicine) in the Australian Register of Therapeutic Goods (the ARTG) which, while a separate and distinct good under subsection 16(1) of the Act, is the same as registered medicine

ZANTAC DOUBLE STRENGTH ranitidine 300mg (as hydrochloride) tablet blister pack (AUST R 95076)

(the "currently registered medicine") except as follows:

- s47 [redacted] has been included as a new drug substance manufacturer.
- The drug substance specification has been updated.
- s47 [redacted] has been added as a new drug product manufacturer.
- The formulation and appearance of the tablets has been changed.
- The drug product specification and analytical methods have been updated.
- The product shelf life has been reduced from 36 months to 24 months (protect from heat/ store below 25°C).
- The labels, Product Information and Consumer Medicine Information have been updated.

PO Box 100 Woden ACT 2606 ABN 40 939 406 804
Phone: 02 6232 8444 Fax: 02 6203 1605 Email: info@tga.gov.au
http://www.tga.gov.au

Decision

As delegate of the Secretary of the Department of Health and Aged Care, I am:

- under subsection 25(3) of the Act, approving the registration of the medicine in the ARTG on the basis that the only difference between the proposed medicine and the currently registered medicine is as described above.
- under subsection 25AB(2) of the Act, notifying you of the decision to register the medicine,
- under subsections 25AA(1) of the Act, approving the text of the PI for the medicine,
- under paragraph 25AB(3)(b) of the Act, notifying you of the approved PI as set out at **Attachment 2**, and
- under subsection 28(2B) of the Act, applying conditions of registration of the medicine, as outlined under '**Conditions of Registration**' below.

Section 25, subsections 25AA(1) and (1A), section 25AB and section 28 of the Act can be found online at the following link: https://www.legislation.gov.au/Series/C2004A03952

Date of effect and supply

Under subsection 16(1) of the Act, the new medicine is a separate and distinct good. However, because you have indicated that the new medicine will replace the existing medicine, the same AUST R number may be used by reason of the Therapeutic Goods (Groups) Order No. 1 of 2001.

The date of effect of the new registration is the date specified in the Certificate of Registration, a copy of which may be obtained via the eBusiness Services (eBS) facilities shortly after receipt of the patent certification requested below. This should be the date included under the heading "date of the most recent amendment" at the end of the approved PI as set out at **Attachment 2**.

Conditions of registration

The conditions applying to the new registration of the medicine are:

1. Conditions applicable to all therapeutic goods as specified in the current edition of the document "Conditions- standard and specific: Applying to registered or listed therapeutic goods under section 28 of the *Therapeutic Goods Act 1989*", and
2. Conditions applicable to the relevant category and class of therapeutic goods as specified in the current edition of the document " Conditions- standard and specific: Applying to registered or listed therapeutic goods under section 28 of the *Therapeutic Goods Act 1989*"

Action required of you

Before the medicine can be included in the ARTG, you are required to either:

- notify the Secretary using the approved form that the patent certification under subsection 26B(1) of the Act is not required in relation to the application; or
- provide a certificate required under subsection 26B(1) of the Act.

Note:

The requirement for patent certificates does not apply to applicants for registration of medicines who are not required to submit evidence or information to establish the safety or efficacy of the goods as part of the registration process. In these circumstances, the applicants are only required

to notify the Secretary in the approved form that the subsection 26B(1) patent certificate is not required in relation to the application.

The notification form and patent certificate can be downloaded via the TGA website (http://www.tga.gov.au/form/australia-united-states-free-trade-agreement). You should forward the completed and signed certificate or notification to otc.medicines@health.gov.au. A certificate of registration can only be issued after receipt of the completed and signed certificate or notification.

Review rights

Details of your review rights are at **Attachment 1**.

Your obligations in relation to Product Information

You are reminded that an approved PI for a medicine cannot be changed without the approval of the Secretary under subsection 25AA(4) of the Act.

You are also reminded that the CMI must comply with the requirements set out in the Therapeutic Goods Regulations 1990 which includes the obligation to ensure the CMI that must be supplied with the medicine is 'consistent with' the approved PI.

Other matters

Copies of the final medicine labels are provided at **Attachment 3**. Please note that your product labels have not been evaluated for compliance with State and Territory labelling requirements.

A copy of the final consumer medicine information is provided at **Attachment 4**.

A copy of the finished product specification is provided at **Attachment 5**.

You are reminded of the pharmacovigilance reporting requirements as set out in the document "*Pharmacovigilance responsibilities of medicine sponsors – Australian recommendations and requirements*", including the requirement to keep the Australian pharmacovigilance contact person details up to date through the TGA Business Services electronic portal.

Please note that it is your responsibility to ensure that current Good Manufacturing Practice clearance letters are maintained for all overseas sites of manufacture registered for the products.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully

Signed and authorised by
s22 [redacted]
Delegate of the Secretary
Complementary & OTC Medicines Branch
s22 [redacted]

17 April 2024

Attachments:

1. Review rights
2. Product information
3. Labels
4. Consumer medicine information
5. Finished product specifications.

Attachment 1

Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of the Act. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of the Act, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: '**decision.review@health.gov.au**'

Subject: "**<insert name of person/company making request>** - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989*"

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "… - Email 1 of 3", "… -

Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of the Act, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of the Act OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

Attachment 2 – Product information

AUSTRALIAN PRODUCT INFORMATION

ZANTAC ranitidine (as hydrochloride) tablets

1. NAME OF THE MEDICINE

Ranitidine hydrochloride.

2. and 3. QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Zantac 150 mg tablets are white film-coated round tablets engraved "150" on one face and plain on the other. The tablets contain 150 mg ranitidine (as hydrochloride).

Zantac 300 mg tablets are white capsule-shaped, film-coated tablets engraved "300" on one face and plain on the other. The tablets contain 300 mg ranitidine (as hydrochloride).

For the full list of excipients, see Section 6.1 List of excipients.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. Short-term treatment of proven duodenal ulcer and gastric ulcer for prophylaxis against recurrent haemorrhage.
2. Maintenance treatment to reduce the risk of relapse in duodenal ulcer.
3. Maintenance treatment for periods up to one year to reduce the risk of relapse in patients with documented healing of benign gastric ulcer.
4. Treatment of gastrinoma (Zollinger-Ellison syndrome).
5. Short-term symptomatic treatment of reflux oesophagitis unresponsive to conservative anti-reflux measures and simple drug therapies such as antacids.
6. Maintenance treatment to reduce the risk of relapse of reflux oesophagitis.
7. Treatment of scleroderma oesophagitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Zantac tablets are administered by mouth.

1. **Acute duodenal or gastric ulceration:**
   300 mg taken as a single dose at bedtime, or 150 mg taken twice daily, in the morning and at bedtime.

   It is not necessary to time the dose in relation to meals. In most cases healing will occur in four weeks although a small number of patients may require an additional 2-4 weeks' therapy.

   Maintenance treatment:
   Duodenal ulcer: 150 mg taken at night.

   As smoking is associated with a higher rate of ulcer relapse, patients should be advised to stop smoking. In patients unable to stop smoking, a dose of 300 mg at night provides additional therapeutic benefit.

   Gastric ulcer: 150 mg taken at night for a period of one year.

2. **Gastrinoma (Zollinger-Ellison syndrome):**
   150 mg taken 3 times daily initially and increased, as necessary, to 600-900 mg/day.

3. **Reflux oesophagitis:**
300 mg taken as a single dose at bedtime or 150 mg taken twice daily in the morning and at bedtime. It is not necessary to time the dose in relation to meals.

In severe reflux oesophagitis the efficacy of 300 mg, taken as a single dose at bedtime, has been established for up to 3 months.

Maintenance treatment:
Reflux oesophagitis: 150 mg taken twice daily in the morning and at bedtime.

4.3 CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastric ulcer
Treatment with a histamine H_2 – antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Zantac tablets is instituted.

Long-term use
The risk of ulcer recurrence is determined by many factors. In some cases, long periods of treatment may be necessary and/or repeated. Evidence from controlled clinical trials of up to 18 months continuous treatment with Zantac has not revealed any undue untoward effects.

Higher doses
The use of higher than recommended doses of intravenous H_2 - antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

Porphyria
Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Zantac should therefore be avoided in patients with a history of acute porphyria.

Gastric pH
Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

Use in renal impairment
Ranitidine is excreted via the kidney and in the presence of renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly in the presence of significant renal impairment, serum levels should be monitored and dosage adjustments made. The clearance of ranitidine is increased during haemodialysis.

Use in the elderly
In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia, A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H_2 – receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1,63 (95% CI, 1,07–2,48).

Paediatric use
Experience with ranitidine tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however, been used successfully in children aged 8–18 years in doses up to 150 mg twice daily.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system:
Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2) Competition for renal tubular secretion:
Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

3) Alteration of gastric pH:
The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

If high doses (2g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of two hours.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no data on the effects of ranitidine on human fertility. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine.

Use in pregnancy
Pregnancy category: B1. The safety of ranitidine in pregnancy has not been established. Ranitidine crosses the placenta. Zantac should only be used during pregnancy if considered essential. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus.

Use in lactation
Ranitidine is secreted in breast milk in lactating mothers, but the clinical significance of this has not been fully evaluated. Zantac should only be used by nursing mothers if considered essential.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 http://www.tga.gov.au/reporting-problems.

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has not been clear in many cases. Headache, sometimes severe, has been reported in a very small proportion of patients.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Rare cases of reversible mental confusion, depression and hallucinations have been reported, predominantly in severely ill and elderly patients. In addition, reversible involuntary movement disorders have been reported rarely. There have been a few reports of reversible blurred vision suggestive of a change in accommodation. Reversible impotence has been reported rarely.

Cardiovascular: As with other H_2 - receptor antagonists rare reports of tachycardia, bradycardia, premature ventricular beats, AV block, and asystole.

Gastrointestinal: Constipation, diarrhoea, nausea/vomiting, abdominal discomfort/pain.

Hepatic: Transient and reversible changes in liver-function tests can occur. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

Musculoskeletal: Rare reports of arthralgias and myalgia.

Haematologic: Rare reports of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplasia have been reported. Blood count changes (leucopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine, no anti-androgenic activity, and cimetidine-induced gynaecomastia and impotence in hypersecretory patients have resolved when ranitidine was substituted. However, occasional cases of breast conditions such as gynaecomastia and galactorrhoea, impotence and loss of libido have been reported in male patients receiving ranitidine but the incidence did not differ from that in the general population.

Integumental: Rash including rare cases of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

Renal: Very rare cases of acute interstitial nephritis have been reported.

Other: Rare cases of hypersensitivity reactions (eg, fever, bronchospasm, anaphylactic shock, urticaria, angioneurotic oedema, hypotension, chest pain, rash, eosinophilia), small increases in serum creatinine. Acute pancreatitis has been reported rarely.

4.9 OVERDOSE

There has been limited experience with overdosage with oral doses of ranitidine. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience. See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS). Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Animal experiments both *in vitro* and *in vivo* have established that ranitidine is a selective, competitive antagonist of histamine at H_2 - receptor sites. Ranitidine has no significant interaction at histamine H_1 - receptors, muscarinic receptors or beta-adrenoceptors. Ranitidine is a potent inhibitor of gastric secretion in the rat and dog.

All the evidence from human studies is compatible with a selective, competitive antagonism of histamine H_2 - receptors by ranitidine in man. Oral administration of ranitidine inhibits both basal gastric secretions and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. On a weight basis ranitidine is between 4 and 9 times more potent than cimetidine.

After oral administration of ranitidine, the plasma concentrations of ranitidine achieved are directly related to the dose administered. A plasma ranitidine concentration of 50-100 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%.

Inhibition of pentagastrin-induced gastric acid secretion increases with dose, being approximately 90% two hours after an oral 150 mg dose and a significant effect is still evident 12 hours after this dose. In 10 patients with duodenal ulcer, 150 mg ranitidine given orally every 12 hours significantly reduced mean 24 hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90% whereas cimetidine (200 mg three times daily and 400 mg at night) reduced mean 24 hour hydrogen ion activity by 48% and nocturnal gastric acid output by 70%.

Pepsin secretion is also inhibited by ranitidine, but secretion of gastric mucus is not affected. Ranitidine does not alter the secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancreozymin. Reduction in gastric acid secretion induced by ranitidine 150 mg twice daily for 7 days did not cause bacterial overgrowth in the stomach.

Pulse rate, blood pressure, electrocardiogram and electroencephalogram were not significantly affected in man following recommended doses of ranitidine.

Chronic ranitidine therapy (300 mg/day for 28 days) had no effect on serum prolactin, gastrin, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone, gonadotrophins, testosterone, oestriol, progesterone or cortisol levels.

One study in 30 male duodenal ulcer patients showed a significant decrease in basal thyroxine levels after 4 weeks' treatment with 300 mg ranitidine daily, but no significant change in thyroid stimulating hormone was noted.

Clinical trials
No clinical trial data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
Peak plasma levels occur about 2-3 hours after oral administration of ranitidine. Absorption is not significantly altered by food or concurrent antacid administration.

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 580 ng/mL) occurred after 1 to 3 hours. Two distinct peaks or a plateau in the absorption phase suggest reabsorption of drug secreted into the intestine. The absolute bioavailability of ranitidine is 50 to 60%, and plasma concentrations increase proportionally with increasing dose up to 200 mg. Bioavailability of ranitidine is

approximately 50%. Serum protein binding of ranitidine in man is in the range 10-19%. The elimination half-life is approximately 2 hours.

Distribution
Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism
The fraction of the dose recovered as metabolites includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide and small amounts of desmethylranitidine and the furoic acid analogue. . The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% after oral administration of the drug.

Excretion
Plasma concentrations decline bi-exponentially, with a terminal half-life of 2 to 3 hours. The major route of elimination of unchanged ranitidine is renal. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Patients over 50 years of age:
In patients over 50 years of age, half life is prolonged (3 to 4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

Impairment of renal function requires a reduction in dosage (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Impairment of liver function may increase the bioavailability of ranitidine but has no significant effect on the elimination half-life, However, in the presence of normal renal function, no dosage reduction for oral or intravenous ranitidine appears necessary in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Croscarmellose sodium, magnesium stearate, microcrystalline cellulose and Opadry II white YS-22-18096.

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, keep dry. Protect from heat.

6.5 NATURE AND CONTENTS OF CONTAINER

Zantac 150 mg tablets are available in Al/Al foil blister packs of 2 (starter packs), 7, 14, 28, 60 and 90 tablets.

Zantac 300 mg tablets are available in Al/Al foil blister packs of 2 (starter packs), 7, 14, 30 tablets.

(Note: Not all strengths or pack sizes are marketed in Australia.)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

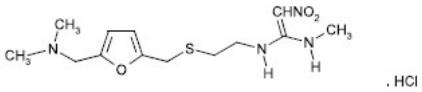
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ranitidine hydrochloride is a histamine H_2 - receptor antagonist. It is an aminoalkyl-substituted furan and is structurally different from cimetidine lacking the imidazole ring and the cyanoguanidine group. Ranitidine hydrochloride is a white to pale yellow granular solid with a melting point of about 140°C. It is freely soluble in water, with a partition co-efficient between n-octanol and water log P = 0.20. It has a slightly bitter taste and sulfurlike odour.

Molecular formula: $C_{13}H_{22}N_4O_3S.HCl$, molecular weight: 350.9, chemical name: N-(2-(((5-((Dimethylamino)methyl)-2-furan-yl)methyl)thio)ethyl)N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride.

Chemical structure:



. HCl

CAS number:
66357-59-3

7 MEDICINE SCHEDULING (POISONS STANDARD)

Prescription Only Medicine (S4):
- Zantac 150 mg tablets: 2, 6, and 60 tablets
- Zantac 300 mg tablets: 2, 4, and 30 tablets

Pharmacy Medicine (S2):
- Zantac 150 mg: 28 tablets
- Zantac 300 mg: 2 and 14 tablets

Not scheduled:
- Zantac 150 mg: 2, 4, 7 & 14 tablets
- Zantac 300 mg: 7 tablets

8 SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street

St Leonards NSW 2065
Australia

9 DATE OF FIRST APPROVAL

Zantac 150 mg tablets [AUST R 53324]: 20/11/1995
Zantac 300 mg tablets [AUST R 53323]: 20/11/1995
Zantac 150 mg (OTC) [AUST R 71786]: 8/11/1999
Zantac Double Strength 300 mg tablets [AUST R 95076]: 11/07/2003

10 DATE OF REVISION

xxxx

Summary table of changes

Section changed	Summary of new information
6.1	Excipient update
6.4	Update to storage temperature and statement
9	Addition of date of first approval of OTC tablet variants.
PI end	Deletion of redundant trademark statement.
All	Deletion of relevant PI information for specific dosage forms other than tablets.
All	General formatting and text insertions for clarity e.g. 'round' in section 2.

Attachment 3 – Labels


Zantac
DOUBLE STRENGTH
14 TABLETS
24 HOUR ACTIVE RELIEF FROM: HEARTBURN ACID INDIGESTION
aspen
Zantac
DOUBLE STRENGTH
ranitidine 300 mg (as hydrochloride)
24 HOUR ACTIVE RELIEF FROM: HEARTBURN ACID INDIGESTION
14 TABLETS EASY TO SWALLOW
New tablet appearance
New formulation
Intended for patients who routinely require two 150 mg ranitidine tablets for the relief of their symptoms.
PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Zantac
DOUBLE STRENGTH
14 TABLETS
Pharma Code
Complete panel required unvarnished for batch details print
ACTIVE INGREDIENT
Each tablet contains ranitidine 300 mg (as hydrochloride)
USE
Effective, long-lasting 24 hour relief from heartburn and acid indigestion due to gastro-oesophageal reflux with one tablet, Zantac Double Strength works by controlling the production of stomach acid. Intended for patients who routinely require two 150 mg ranitidine tablets for the relief of their symptoms.
WARNINGS
Do not use if under 12 years of age unless directed to do so by your doctor.
This preparation is for relief of minor and temporary ailments and should be used strictly as directed.
Do not use, except on doctor's advice, with aspirin or other anti-inflammatory medicines or for any purpose other than specified on the pack.
If symptoms persist or recur within two weeks, or if new or additional symptoms occur, consult a doctor.
If breastfeeding or pregnant, or likely to become pregnant, consult a pharmacist or a doctor before use.
DIRECTIONS FOR USE
Adults and children over 12 years: Swallow 1 tablet whole (do not chew) with water as soon as you have symptoms, at any time day or night. Maximum 1 tablet in 24 hours. Do not use for more than 14 days continuously.
OTHER INFORMATION
Store below 25°C. Protect from heat.
continued
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34-36 Chandos Street St Leonards
NSW 2065 Australia
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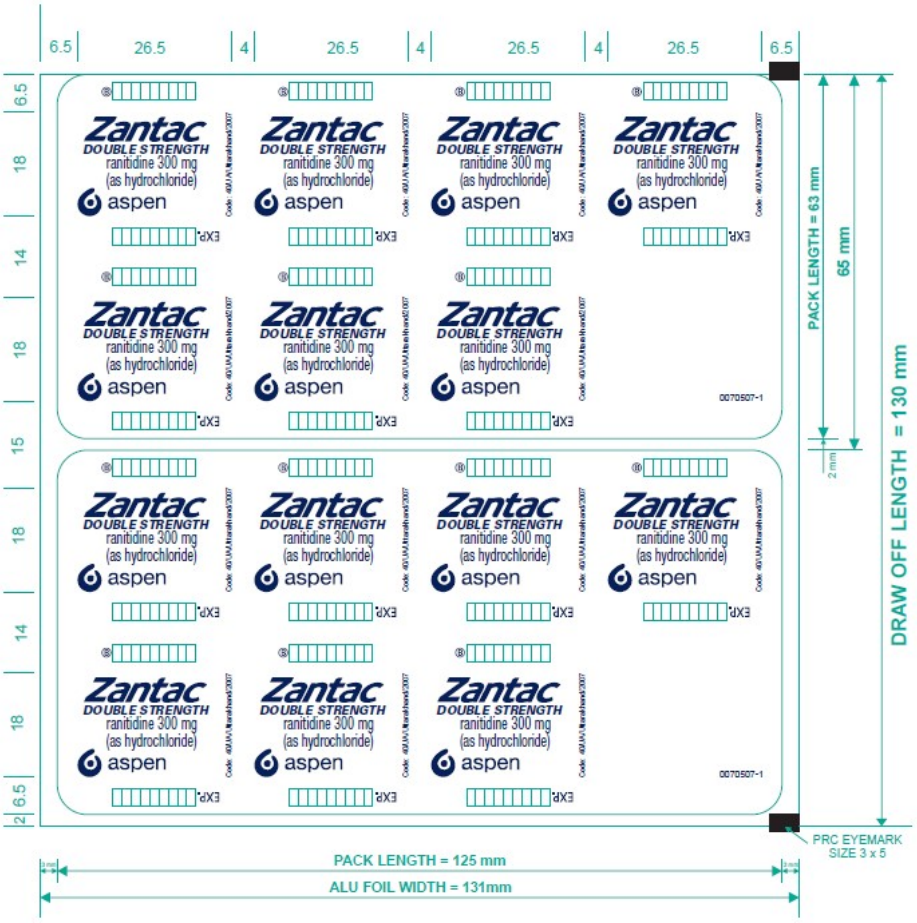
X XXXXXX XXXXXX


6.5
26.5
4
26.5
4
26.5
4
26.5
6.5
Zantac
DOUBLE STRENGTH
ranitidine 300 mg
(as hydrochloride)
aspen
EXP.
0070507-1
PACK LENGTH = 63 mm
65 mm
2 mm
DRAW OFF LENGTH = 130 mm
PRC EYEMARK
SIZE 3 x 5
PACK LENGTH = 125 mm
ALU FOIL WIDTH = 131mm

Attachment 4 – CMI

Zantac tablets

ranitidine hydrochloride

Consumer Medicine Information (CMI)

About your Zantac tablets

Read all of this leaflet carefully before you take your medicine.

This leaflet does not have the complete information available about your medicine. If you have any questions about your medicine, you should ask your doctor or pharmacist.

All medicines have some risks. Sometimes new risks are found even when a medicine has been used for many years.

If there is anything you do not understand, ask your doctor or pharmacist. If you want more information, ask your doctor or pharmacist.

What is in my Zantac?

The medicine in your Zantac tablets is called ranitidine (as hydrochloride). This belongs to a group of medicines called H2-antagonists.

What does my Zantac do?

Zantac is mostly used to:

- treat stomach and duodenal ulcer disease (also known as peptic ulcer);
- stop these ulcers from coming back;
- treat reflux oesophagitis (also known as reflux).

These problems are caused, in part, by too much acid in the stomach. This can lead to pain such as heartburn. Zantac works by reducing the amount of acid in the stomach. This reduces the pain and also allows the ulcer and reflux to heal.

Zantac is also used to treat Zollinger-Ellison disease.

Zantac 150 mg and 300 mg tablets are either available with a doctor's prescription (for larger pack sizes) or from a pharmacist (for smaller pack sizes).

Before you take it

Do not take if:

You must not take Zantac if:

- you have ever had an allergic (hypersensitive) reaction to ranitidine or any of the ingredients listed towards the end of this leaflet.
- the expiry date (EXP) printed on the pack has passed.
- the packaging is torn or shows signs of tampering.

Tell your doctor if:

You must tell your doctor if:

- you are allergic to foods, dyes, preservatives or any other medicines
- you have ever had an allergic (hypersensitive) reaction to ranitidine or any of the ingredients listed towards the end of this leaflet.
- you are allergic to any medicine,
- you have stomach cancer,
- you have kidney disease,
- you have had stomach ulcers before and you are taking Non-Steroidal Anti-Inflammatory (NSAID) medicines.
- you have a disease known as acute porphyria.
- you are over 65 years of age.
- you have lung disease.
- you are diabetic.
- you have any problems with your immune system.
- you have to stop taking this or any other medicine for your ulcer or reflux.

Taking other medicines

Tell your doctor or pharmacist if you are taking any other medicines, have taken any recently, or if you start new ones. This includes herbal medicines and any other medicines you have bought without a prescription.

Zantac can affect the way some other medicines work. Also other medicines can affect the way Zantac works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:

- warfarin, used to prevent blood clots
- triazolam and midazolam, used as sedatives
- ketoconazole, an anti-fungal
- atazanavir and delaviridine, used to treat HIV

- glipizide, used for diabetics.
- gefitinib, used in the treatment of cancer.
- Non-Steroidal Anti-Inflammatory (NSAID) medicines, for pain and inflammation
- procainamide or n-acetylprocainamide, used to treat heart problems
- sucralfate used to treat ulcers.

What if I am pregnant or breast feeding?

Tell your doctor if you are pregnant, likely to get pregnant or are breast feeding. Your doctor will tell you if you should take this medicine.

How do I take it

- The dosage depends on the disease that you are suffering from. Your doctor or pharmacist will usually tell you how many Zantac tablets to take and how often to take them. You will also find this information on the label of your medicine.
- The normal adult dosage is 150 to 300 milligrams per day, taken as one 150 mg tablet once or twice a day, or one 300 mg tablet at bedtime. Your doctor may prescribe a different dosage.
- Do not take extra tablets. Do not take the tablets more often than you have been told.
- It does not matter whether you take the tablets before or after food.
- Zantac tablets should be swallowed whole with a glass of water.
- Your pain or other symptoms may take a few days to go away.
- Take all the tablets your doctor has prescribed for you, even if you feel better.
- Even when you have completed your tablets, your doctor may decide to continue your treatment with Zantac, possibly at a different dosage, in order to prevent the problem coming back again.

Use in Children:

Zantac has not been studied fully in children. However, Zantac has been used with good results in children aged 8 to 18 years in doses up to 150 mg twice daily.

What should I do if I miss my dose?

If you forget to take your Zantac, take another as soon as possible unless it is nearly time for your next dose. Do not take a double dose to make up for the missed one.

Side effects

Like other medicines, Zantac may cause some side-effects. Most of the side-effects will be minor and temporary, but some may be serious. Your doctor will be able to answer any questions you may have.

Tell your doctor straight away and do not take any more Zantac if you have:

- an allergic reactions, the signs may include:
  - skin reactions such as rash (red spots), itching, skin lumps or hives
  - swelling of the eyelids, face, lips, tongue or other parts of the body
  - shortness of breath, trouble breathing, wheezing, chest pain or tightness
  - unexplained fever and feeling faint, especially when standing up.
- severe stomach pain or a change in the type of pain,
- yellow colouring of the skin or eyes (jaundice),confusion,
- general illness associated with weight loss,
- fever.
- irregular heart beat (including unusually fast or slow heart beats),
- changes to heart beat.

If you get any of the following side-effects after taking Zantac tell your doctor, but there is no immediate reason to stop taking the tablets unless you are concerned:

- headache,
- joint or muscle pains,
- dizziness,
- depression,
- constipation
- feeling sick (nausea) or vomiting
- diarrhoea
- breast tenderness and/or breast enlargement
- breast discharge.
- changes in liver function tests

If you notice any symptoms that concern you or if the tablets cause any other side-effects, tell your doctor or pharmacist.

If you have taken all the tablets and still do not feel better tell your doctor as soon as possible.

Other side effects not listed above may also occur in some people.

Overdose

In the event of an overdose you should immediately telephone your doctor or Poisons Information Centre (telephone 131126) for advice, if you think you or anyone else may have taken too much Zantac, even if there

are no signs of discomfort or poisoning. If you are not sure what to do, contact your doctor or pharmacist.

How do I store my Zantac?

- Store below 25°C, keep dry. Protect from heat.
- Keep Zantac tablets in a place where children cannot reach them.
- You will find an "expiry" (or use by) date printed on the manufacturer's label of the pack. Do not use the tablets after this date. Do not use the tablets if they are discoloured.
- Leave the tablets in the pack until you are ready to use them.

Can I let someone else use my Zantac?

Never give this medicine to someone else. The medicine is only for you. It may harm other people even if they seem to have the same symptoms that you have.

Product description

What Zantac tablets look like.

Zantac tablets come in two strengths:

150 mg - white, film coated, round tablets engraved '150' on one face and plain on the other. Available in packs of 14 tablets (from your pharmacy) or 60 tablets (from your doctor).

300 mg - white, capsule shaped, film coated tablets engraved '300' on one face and plain on the other. Available in packs of 14 tablets (from your pharmacy) or 30 tablets (from your doctor).

(Not all pack sizes are marketed.)

Ingredients

Zantac contains the active ingredient ranitidine (as ranitidine hydrochloride). Each tablet contains either 150 or 300 milligrams of ranitidine.

They also contain the inactive ingredients:

microcrystalline cellulose, magnesium stearate, croscarmellose sodium and Opadry II white YS-22-18096

Zantac tablets are free from gluten and lactose.

Who makes my Zantac?

Aspen Pharmacare Australia Pty Ltd

34-36 Chandos Street

St Leonards NSW 2065

Australia.

Australian Registration Numbers:

Zantac 150 mg tablets: AUST R 53324

Zantac 300 mg tablets: AUST R 53323

Zantac 150 mg tablets (OTC): AUST R 71786

Zantac DOUBLE STRENGTH 300 mg tablets (OTC): AUST R 95076

This leaflet was revised in February 2024.

Attachment 5 – Finished product specification

s47 [redacted]

PRODUCT RELEASE SPECIFICATION

Product Name : Ranitidine Tablets 300 mg			
Standard	: IH	Reference	: BP/Ph.Eur/IH
Code No.	: 2005550	Specification No.	: 2005550/PRS/R4
Effective Date	: Draft Spec	Page No.	: 1 of 3
Shelf life	: 24 Months	Supersedes	: 2005550/PRS/R3
Market / Customer: Australia/Aspen Pharmacare			

REASON FOR REVISION:

Revision No.	Changes incorporated	Effective Date
R 1	New Specification introduced.	27-Mar-2017
R 2	Change in the assay limit from "Not less than 98.0 % and not more than 105.0 % (Not less than 294.0 mg and not more than 315.0 mg)" to "Not less than 95.0 % and not more than 105.0 % (Not less than 285.0 mg and not more than 315.0 mg)" in the In-process Specification (Lubricated granules) as per change control number: PC-PYD/2017/101	10-Apr-2017
R 3	Change in organization name as per change control number PC-CRP/2018/063. Inclusion of note under footnote in PRS and SLS. Inclusion of Related Substances by LC-HRMS (For NDMA impurity) test in PRS and SLS,Changes done as per change control number PC-TSG/2019/357.	22-Nov-2019
R4	Change in reference STP number as per SOP-GQC/052 due to introduction of STP into LIMS. Change in format as per SOP-GQC/053. Updation of storage, shelf life, market/customer name. Updation of specification limit for N-Nitrosodimethylamine (NDMA Impurity) under Related Substances by LC-HRMS test in PRS and SLS stages. Updation of specification limit for Impurity 1(Impurity H), Impurity 2 (Impurity C) , Impurity 3 (Impurity E), Impurity 4 (Impurity D), Total impurities (Not including impurity A) under Related substances by UPLC test in PRS and SLS stages. Inclusion of Impurity A under Related substances by UPLC test in PRS and SLS stages. Removal of footnote related to Related Substances by LC-HRMS test from PRS and SLS stages. Changes done as per record number: 417349.	Draft

GQC/053/F-09/R1

s47 [redacted]

PRODUCT RELEASE SPECIFICATION

Product Name : Ranitidine Tablets 300 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005550	Specification No. : 2005550/PRS/R4
Effective Date : Draft Spec	Page No. : 2 of 3
Shelf life : 24 Months	Supersedes : 2005550/PRS/R3
Market / Customer: Australia/Aspen Pharmacare	

S No.	Test	Specification limits	Test method
1	Description	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	ASD/GP/0362
2	Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	IH
3	Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	IH
4	Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	BP
5	Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	IH
6	Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	ASD/GP/0424
7	Related substances by UPLC		IH
	i) Impurity A	Not more than 0.5%	
	ii) Impurity 1 (Impurity H)	Not more than 0.2%	
	iii) Impurity 2 (Impurity C)	Not more than 0.2%	
	iv) Impurity 3 (Impurity E)	Not more than 0.2%	
	v) Impurity 4 (Impurity D)	Not more than 0.2%	
	vi) Largest single unknown impurity	Not more than 0.2%	
	vii) Total impurities (Not including impurity A)	Not more than 1.0%	
8	Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	IH
		Label claim Limit	
	Assay in %	300 mg - Not less than 98.0 % and not more than 105.0 %	
	Assay in mg	300 mg - Not less than 294.0 mg and not more than 315.0 mg	

GQC/053/F-09/R1

s47

PRODUCT RELEASE SPECIFICATION

Product Name : Ranitidine Tablets 300 mg			
Standard : IH		Reference : BP/Ph.Eur/IH	
Code No. : 2005550		Specification No. : 2005550/PRS/R4	
Effective Date : Draft Spec		Page No. : 3 of 3	
Shelf life : 24 Months		Supersedes : 2005550/PRS/R3	
Market / Customer: Australia/Aspen Pharmacare			
9	Microbial limits		ASD/GP/0539
	i) Total aerobic microbial count	Not more than 1000 cfu/g	
	ii) Total combined yeast & molds count	Not more than 100 cfu/g	
	iii) Escherichia coli	Absent/1 g	
10	Related Substances by LC-HRMS		IH
	i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than s47	

Reference STP No.: 2005549/FPSTP

STORAGE: Store below 25° C. Protect from heat.

PACKING :
Not Applicable

NOTE :
i) IH refers to In-house.
ii) Report Assay value in both Percentage and Milligram.
iii) Residual solvents : Based on the information provided by the suppliers, only Class 2 and / or Class 3 solvents are likely to be present in the ingredients used to manufacture this product. The cumulative quantity of the solvents, contributed by all the ingredients are within the limit and the manufacture process of the product does not include any solvent. Since the Residual solvents are within the limits specified in the ICH guideline Q3C (Option 1) in the Finished Product, these solvents are not tested.
iv) Microbial limits test will be performed on initial three batches and on every 10th batch manufactured or once per year, whichever falls first for monitoring purpose only (for information) and not for product release criteria.

s22

GQC/053/F-09/R1

s47 [redacted]

SHELF LIFE SPECIFICATION

Product Name : Ranitidine Tablets 300 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005550	Specification No. : 2005550/SLS/R4
Effective Date : Draft Spec	Page No. : 1 of 3
Shelf life : 24 Months	Supersedes : 2005550/SLS/R3
Market / Customer: Australia/Aspen Pharmacare	

REASON FOR REVISION:

Revision No.	Changes incorporated	Effective Date
R 1	New Specification introduced	27-Mar-2017
R 2	Change in the assay limit from "Not less than 98.0 % and not more than 105.0 % (Not less than 294.0 mg and not more than 315.0 mg)" to "Not less than 95.0 % and not more than 105.0 % (Not less than 285.0 mg and not more than 315.0 mg)" in the In-process Specification (Lubricated granules) as per change control number: PC-PYD/2017/101	10-Apr-2017
R 3	Change in organization name as per change control number PC-CRP/2018/063. Inclusion of note under footnote in PRS and SLS. Inclusion of Related Substances by LC-HRMS (For NDMA impurity) test in PRS and SLS,Changes done as per change control number PC-TSG/2019/357.	22-Nov-2019
R4	Change in reference STP number as per SOP-GQC/052 due to introduction of STP into LIMS. Change in format as per SOP-GQC/053. Updation of storage, shelf life, market/customer name. Updation of specification limit for N-Nitrosodimethylamine (NDMA Impurity) under Related Substances by LC-HRMS test in PRS and SLS stages. Updation of specification limit for Impurity 1(Impurity H), Impurity 2 (Impurity C), Impurity 3 (Impurity E), Impurity 4 (Impurity D), Total impurities (Not including impurity A) under Related substances by UPLC test in PRS and SLS stages. Inclusion of Impurity A under Related substances by UPLC test in PRS and SLS stages. Removal of footnote related to Related Substances by LC-HRMS test from PRS and SLS stages. Changes done as per record number: 417349.	Draft

GQC/053/F-09/R1

s47 [redacted]

SHELF LIFE SPECIFICATION

Product Name : Ranitidine Tablets 300 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005550	Specification No. : 2005550/SLS/R4
Effective Date : Draft Spec	Page No. : 2 of 3
Shelf life : 24 Months	Supersedes : 2005550/SLS/R3
Market / Customer: Australia/Aspen Pharmacare	

S No.	Test	Specification limits	Test method
1	Description	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	ASD/GP/0362
2	Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	IH
3	Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	IH
4	Related substances by UPLC		IH
	i) Impurity A	Not more than 0.5%	
	ii) Impurity 1 (Impurity H)	Not more than 0.2%	
	iii) Impurity 2 (Impurity C)	Not more than 0.2%	
	iv) Impurity 3 (Impurity E)	Not more than 0.2%	
	v) Impurity 4 (Impurity D)	Not more than 0.2%	
	vi) Largest single unknown impurity	Not more than 0.2%	
	vii) Total impurities (Not including impurity A)	Not more than 1.0%	
5	Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	IH
		Label claim Limit	
	Assay in %	300 mg - Not less than 95.0 % and not more than 105.0 %	
	Assay in mg	300 mg - Not less than 285.0 mg and not more than 315.0 mg	
6	Microbial limits		ASD/GP/0539
	i) Total aerobic microbial count	Not more than 1000 cfu/g	
	ii) Total combined yeast & molds count	Not more than 100 cfu/g	
	iii) Escherichia coli	Absent/1 g	
7	Related Substances by LC-HRMS		IH
	i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.32 ppm	

GQC/053/F-09/R1

s47 [redacted]

SHELF LIFE SPECIFICATION

Product Name : Ranitidine Tablets 300 mg	
Standard : IH	Reference : BP/Ph.Eur/IH
Code No. : 2005550	Specification No. : 2005550/SLS/R4
Effective Date : Draft Spec	Page No. : 3 of 3
Shelf life : 24 Months	Supersedes : 2005550/SLS/R3
Market / Customer: Australia/Aspen Pharmacare	

Reference STP No.: 2005549/FPSTP

STORAGE: Store below 25° C. Protect from heat.

PACKING :
Not Applicable

NOTE :
i) IH refers to In-house.
ii) Report Assay value in both Percentage and Milligram.
iii) Microbial limits test to be performed for accelerated stability samples at initial and end of the study, for long term stability samples at initial and thereafter annually once

s22 [redacted]

GQC/053/F-09/R1

s47F

From: s22
Sent: Thursday, 18 April 2024 3:24 PM
To: s22
Cc: TGA Nitrosamines
Subject: Notice of revocation of suspension - OTC ranitidine product - AUST R 95076 Zantac Double Strength - Final [SEC=UNOFFICIAL]
Attachments: Notice of revocation OTC ranitidine product AUST R 95076 Zantac Double Strength.pdf

Dear s22

Please find attached the revocation of suspension notice for the Zantac Double Strength product.

Regards
s22

OM-2023-00902 & 00903-1 - Aspen Pharmacare Australia Pty Ltd –

ZANTAC DOUBLE STRENGTH ranitidine 300mg (as hydrochloride) tablet blister pack - C2 – 95076, FN 2013/011102

ZANTAC ranitidine 150mg (as hydrochloride) tablet blister pack (OTC) - C2 – 71786, FN 2013/011101

FNs: see above
Edata: D23-4157504 & D23-4157500
Sequence: e003296(0014)

Background

The company's cover letters (dated 10 November 2023) are included below.

OM-2023-00902-1 e003296 (0014) - C2

OM-2023-00903-1 e003296 (0014) - C2

The company propose to:

- Include s47 as a new drug substance manufacturer.
- Update the drug substance specification.
- Include s47 as a new drug product manufacturer.
- Change the formulation and appearance of the tablets.
- Update the drug product specification and analytical methods.
- Reduce the tablet shelf life from 36 months to 18 months (store below 25°C).
- Update the labels, PI and CMI.

The change codes are:

- GEX – change in the amount of an excipient (if grouping applies) – s23.
- QSX – more restrictive drug substance specification limits – O.
- QST – addition of drug substance specification test – O.
- QSS – change of drug substance manufacturer – O.
- MMA – addition of a finished product manufacturer – CN – 9D(2C).
- MPR – manufacturing process changes – C1 – 9D(3).
- QFX – more restrictive finished product specification limits or requirements – O.
- QFT – addition of an extra finished product specification test - O
- QFC – finished product analytical method change – C2 – 9D(3).
- Labels/ PI/ CMI?

Relevant BP and USP monographs are included below.

Ranitidine Hydrochloride - British

Ranitidine Tablets - British Pharmacopoeia

USP-NF Ranitidine Hydrochloride.pdf

USP-NF Ranitidine Tablets.pdf

Assurance was provided that no other quality aspects of the product have been altered.

Evaluation

The proposed changes are intended to control nitrosamine levels in the drug substance and drug products to levels in line with TGA (Appendix 1 - Established acceptable intake for nitrosamines in medicines | Therapeutic Goods Administration (TGA)) and EMA recommendations. The sponsor argues that the only relevant nitrosamine that may be present in the drug products is N-nitroso dimethylamine, which has an acceptable intake (AI) of 96.0 ng/day.

The changes described below have also been proposed for the prescription variants of the OTC tablets. The submission numbers for the prescription medicine applications are PM-2023-05321, 05322, 05323 and 05324-1 and the relevant file is 2012/021274. The OTC assessment will rely on the PSC evaluation (D24-91204).

Drug substance changes

It was stated that the current drug substance supplier s47 will be replaced by s47 s47 . The manufacture and quality control of the drug substance at this site are covered by an EDQM certificate of suitability (R1-CEP s47). Comparative impurity data from both the proposed and approved drug substance manufacturing sites were provided. Also, an assessment of NDMA levels in 8 batches of the drug substance from the proposed site showed the highest levels detected were s47 . Comparative particle size analysis and finished product dissolution data were also provided.

Updated drug substance specifications from the drug substance manufacturer s47 and the finished product manufacturer were provided. The updated specification includes a limit for NDMA of NMT s47 . It was argued that the route of synthesis used by s47 precludes the formation of other nitrosamines. The Prescription Medicines evaluation did not raise any issues with the changes to the drug substance.

Formulation changes and changes to the tablet appearance

The following formulation changes are proposed for the 150 mg tablets:

- The quantity of microcrystalline cellulose/ tablet will be reduced, from s47 to s47 .
- Croscarmellose sodium (s47 / tablet) will be added to the formulation.
- The amount of MgSt/ tablet will be increased from s47
- The type and amount of Opadry coating will change from Opadry II white YS-S-7322 (13.50 mg/ tablet) to Opadry II white YS-22-18096 (14.25 mg/tablet).

In conjunction with the these changes the description of the tablets will change from 'White, film coated, round tablet, engraved on one side with "150" and plain on the other' to 'White, film coated, biconvex tablet, engraved on one side with "RAN 150" and plain on the other'

The following formulation changes are proposed for the 300 mg tablets:

- The quantity of microcrystalline cellulose/ tablet will be increased from s47 to s47 .
- The quantity of croscarmellose sodium/ tablet will be increased from s47 mg.
- The quantity of MgSt/ tablet will be increased from s47
- The type and amount of Opadry coating will change from Opadry II white YS-S-7322 (19.20 mg/ tablet) to Opadry II white YS-22-18096 (28.5 mg/tablet).

In conjunction with these changes the description of the tablets will change from 'White, film coated, round tablet, engraved on one side with "300" and plain on the other' to 'White, film coated, biconvex tablet, engraved on one side with "RAN 300" and plain on the other'.

Note that with the proposed changes to the tablet formulations, the 150 mg and 300 mg strengths become direct scales and the Prescription Medicines evaluation has opined that the proposed formulation changes do not require supportive bioequivalence data. However, it was also noted that, whilst the proposed changes to the 300 mg tablet strength are covered by the Grouping Order, the changes to the 150 mg strength tablet (with the addition of a new excipient) are not covered. **Therefore the application for the 150 mg strength tablet needs to be withdrawn and resubmitted as an N3 (abridged) application.**

The PARs have already been updated, for both products.

Drug product manufacturer and manufacturing process changes
The new drug product manufacturer will be s47 – GMP clearance MI-2023-CL-09737-1, expires 24/8/2026. The current manufacturer is s47. **The PARs have already been updated.**

The method of manufacture at the new site is similar to the one used at the old one but an additional s47 batch size has been added to the approved s47 batch size for the 150 g strength tablets and the s47 batch size for the 300 mg strength tablets. The Prescription Medicines assessment has accepted the manufacturing process and batch size.

Drug product specification and analytical method changes.
The proposed drug product specification for the 150 mg tablets is at e003296 (0015-) - Specification and the proposed drug product specification for the 300 mg tablets is at e003296 (0015-) - Specification.

The following points are noted with regard to both specification documents:

- Two additional identity tests, by TLC and a chemical test for chlorides, have been added to the release specifications.
- The disintegration test has s47.
- The assay release limit has been tightened to 97.0 – 105.0%. The assay expiry limit remains at 95.0 – 105.0%.
- The related substances limits have been significantly revamped. The current specification includes limits for any single highest impurity – NMT 0.5%, any secondary single highest impurity – NMT 0.3% and total impurities NMT 1.2%. The proposed specifications nominate BP Impurities H, C, E and D (each NMT 0.3% at release and expiry) and the largest single unknown impurity (NMT 0.2% at release and expiry), with total impurities NMT 2.0%.
  Neither the current or proposed limits are matched with those in the BP product monograph, which specifies BP Impurity A (NMT 0.5%), any secondary single impurity (NMT 0.2%) and total impurities, however the limits are in line with those specified by the USP product monograph (which uses a TLC test). **As a result of the Prescription Medicines evaluation, the drug product specification has been updated so that the related substances limits are aligned with those in the BP monograph. The updated 150 mg tablet and 300 mg tablet drug product specifications are included below.**

  fps 150.pdf fps 300.pdf

- Limits for NDMA of NMT s47 at release and NMT 0.32 ppm at expiry have been introduced.

In conjunction with the proposed related substance specification limit changes a new UPLC analytical method has be introduced and the method has been accepted by the Prescription Medicines evaluator.

Shelf life and storage condition changes
The company propose to reduce the products' shelf lives from 36 months to 18 months (store in a dry place and protect from heat). However, as part of the Prescription Medicines assessment, the products have been approved with a 24 month shelf life (Protect from heat. Store below

25°C). **The PARs have been updated for the 150 mg strength product and sponsor verification is required.**

Labels
The approved pack sizes for the 300 mg product are 2, 7 and 14 tablets/ carton and the approved pack sizes for the 150 mg product are 2, 4, 7, 14 and 28 tablets.

According to the SUSMP, ranitidine 150 mg tablets are unscheduled when they are in containers containing 14 tablets or less. The ranitidine 300 mg tablets are unscheduled when they are in containers with 7 tablets or less. The ranitidine tablets containing NMT than 14 days supply are in Schedule 2 of the SUSMP. So the 14 tablet presentation for the 300 mg product and the 28 tablet presentation for the 150 mg product are in Schedule 2; the rest are unscheduled.

Both the SUSMP and RASML require the following warning statement:
'This preparation is for the relief of minor and temporary ailments and should be used strictly as directed. If symptoms persist or recur within two weeks, consult a doctor.'

The proposed labels were compared with the approved ones (at D18-10098882). The storage conditions have been changed from 'Store below 30°C. Keep dry.' to 'Store below 25°C, keep dry. Protect from heat. Otherwise, the information on the proposed labels is identical to that on the approved labels.

OTC advice (D24-1351344) was sought regarding the acceptability of the tradenames for the 300 mg tablet strength and, while the ZANTAC DOUBR STRENGTH name was accepted, inevitable problems with the labels were identified. The company was asked to modify the labels in the following manner (D24-1418018):

- For the 300 mg tablet a prominent statement is required on the main carton label that the medicine is intended for use by patients who currently require two 150 mg ranitidine tablets for relief of their symptoms. The statement should be presented in such a way that it clearly stands out to prospective purchasers.

- The directions for use for the 150 mg tablet should be modified to 'Take one at the first sign of symptoms. If symptoms return or persist for more than one hour, take another tablet. Do not take more than 2 tablets in 24 hours.

The updated labels (D24-1418159 andD24-1418195) are included below.
150 mg:


SUB_CTN_Zantac_Ta bs_150mg_7s_P_INDI


SUB_CTN_Zantac_Ta bs_150mg_14s_P_INC


SUB_CTN_Zantac_Ta bs_150mg_28s_P_INC


SUB_FOIL_Zantac_TA B_150mg_P_EXT.pdf

300 mg:


SUB_CTN_Zantac_Ta bs_Double_Strength_3


SUB_CTN_Zantac_Ta bs_Double_Strength_3


SUB_FOIL_Zantac_TA B_300mg_P_EXT.pdf

PI
The updated PI is included below.

pi.pdf

CMI
The updated CMI is included below.

cmi.pdf

Recommendation
Approval of the 150 mg tablet application is approved based on the Prescription Medicines assessment. As noted above, the 300 mg tablet submission will need to be resubmitted as an N3 (abridged) application.

s22 [redacted]
3/4/2024

OM-2024-00299-1 - Aspen Pharmacare Australia Pty Ltd - ZANTAC ranitidine 150mg (as hydrochloride) tablets - N3
FN E24-147431
Sequence e003296(0018)
Edata D24-1334459

The C2 application (OM-2023-00903-1) for the 150 mg strength tablet has been withdrawn and a new N3 abridged application has been submitted in its place. The cover letter for this application (dated 10 April 2024) is included below.

cover.pdf

Recommendation
Approval is recommended based on the information provided in the now withdrawn OM-2023-00903-1 application (see details above).

s22 [redacted]
17/4/2024

s47F

From: s22
Sent: Thursday, 18 April 2024 3:24 PM
To: s22
Cc: TGA Nitrosamines
Subject: Notice of revocation of suspension - OTC ranitidine product - AUST R 95076 Zantac Double Strength - Final [SEC=UNOFFICIAL]
Attachments: Notice of revocation OTC ranitidine product AUST R 95076 Zantac Double Strength.pdf

Dear s22

Please find attached the revocation of suspension notice for the Zantac Double Strength product.

Regards
s22

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Aspen Pharmacare Australia Pty Ltd
s22 [redacted] @aspenpharmacare.com.au

s22 [redacted]

Notice of revocation of suspension of the registration of therapeutic goods

Dear Sir/Madam

I refer to the following therapeutic goods, which are registered in relation to Aspen Pharmacare Australia Pty Ltd in the Australian Register of Therapeutic Goods (the ARTG):

- 95076 - ZANTAC DOUBLE STRENGTH ranitidine 300mg (as hydrochloride) tablet blister pack

(**your medicine**)

Decision maker

I am a delegate of the Secretary of the Department of Health for the purposes of section 29F of the *Therapeutic Goods Act 1989* (**the Act**).

Result of my decision

In accordance with subsection 29F(1) of *the Act*, I am writing to inform you that I am revoking the suspension of the registration of the above therapeutic good, which is the subject of this notice (**your medicine**). My reasons for this decision are set out below.

Background

Between September and November 2019, the European Directorate for the Quality of Medicines (**EDQM**) suspended all certificates of suitability to the monographs of the European Pharmacopoeia (**CEP**) for ranitidine hydrochloride. At the time your medicine was registered, you provided a CEP as evidence of the quality of the ranitidine drug substance in your medicines. In response to the TGA's section 31 request for information, dated 22 October 2019, you indicated that you do not have any alternative sources of ranitidine hydrochloride registered for **your medicine**.

I refer to the previous communications between the TGA and you regarding the TGA's concerns with the contamination of ranitidine products with *N*-nitrosodimethylamine (NDMA). In previous correspondence, you were notified of the TGA's proposal and subsequent decision to suspend the registration of **your medicine**, under paragraph 29D(1)(b) of *the Act*, as these relied on a suspended certificate of suitability (**CEP**).

Suspension of a CEP by the EDQM indicates to the TGA that the supporting evidence of satisfactory drug substance manufacture and control (i.e. the quality) is no longer acceptable. It is therefore likely that the quality of the drug substance manufactured by a manufacturer who has sought to rely on a CEP that has been suspended is unacceptable.

Following the above decision you submitted an application dated 10 November 2023 under Section 23 of *the Act* to register a new formulation for **your medicine**. The new formulation, while considered separate and distinct, the medicine currently once registered, was able to maintain the same registration number (AUST R 95076) as the changes made were consistent with the provision of the Therapeutic Goods (Groups) Order No. 1 of 2001. A decision was made to approve this application on 17 April 2024 (TGA reference D23-4564557).

Material considered

In making this decision, I have considered the following information:

1. The ARTG entries for **your medicine**, including information on the drug substance manufacturing site.
2. Your application dated 10 November 2023 (OM-2023-00902-1)
3. Information available on the status of CEPs within the EDQM database[1].

Reasons for Decision

You submitted an application dated 10 November 2023 under Section 23 of *the Act* to register a new formulation for **your medicine** along with other changes. These changes are listed below:

a. Changes to the drug product formulation
    i. Change to the quantities of excipients croscarmellose sodium, microcrystalline cellulose and magnesium stearate.
    ii. Change from film coating material Opadry II white YS-S-7322 to Opadry II white YS-22-18096
b. Addition of alternative drug substance site of manufacture:
    s47 [redacted] (Steps: ACT)
c. Changes to the drug substance specification – including test and limits for NDMA.
d. Addition of the following alternative drug product site of manufacture:
    s47 [redacted]
    Steps: MDD, MXP, MXR, QUAL, TCC and TMM
e. Cessation of the following site of manufacture:
    s47 [redacted]

[1] https://extranet.edqm.eu/4DLink1/4DCGI/Query_CEP?vSelectName=1&Case_TSE=none&vContains=1&vContainsDate=1&vtsubName=ranitidine&vtsubDateBegin=&vtsubDateBtwBegin=&vtsubDateBtwEnd=&SWTP=1&OK=Search

s47 [redacted]

f. Changes to the drug product manufacture – addition of alternative batch size for bulk granule s47 [redacted]
g. Changes to the drug product specifications – including new in-house UPLC method for related substances.
h. Reduction of the drug product shelf-life to 24 months 'Store below 25°C, Store in dry place, protect from heat'.
i. Consequential changes to product labels, PI and CMI.

Based on the material considered, the changes listed above, which were approved on 17 April 2024, are considered to resolve the issues that have been presented in the section titled **Background**, in that the source of ranitidine hydrochloride was not considered suitable for use and the CEP in place had been suspended. It is noted a new CEP has been included in the registration (point c) which is valid, to replace the suspended CEP that the suspension of the license was based on.

Therefore, I have decided to revoke the suspension of the registration of **your medicine** listed above as I am satisfied that the grounds on which the registration was suspended no longer applies and that there are no new grounds to suspend the registration of the therapeutic goods.

Date of effect and period of suspension

The revocation of the suspension will take effect from the date of this letter.

The TGA will cause to be published on the Department's website a notice setting out the particulars of the revocation.

Appeal provisions

This decision is a reviewable initial decision under section 60 of *the Act*. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision. Information on how to request a reconsideration of this decision is provided in **Attachment 1**.

Please do not hesitate to contact me if you have any further queries regarding this matter.

Yours faithfully,

Signed and authorised by
s22 [redacted]
Delegate of the Secretary
Complementary & OTC Medicines Branch
s22 [redacted]@health.gov.au
18 April 2024

Attachment 1 - Request for reconsideration of an initial decision

This decision is a reviewable initial decision under section 60 of *the Act*. Under section 60, a person whose interests are affected by a 'reviewable' initial decision, can seek reconsideration of the initial decision.

As this document constitutes written notice of the making of an initial decision being given by the Secretary, a request for reconsideration of this initial decision must be given to the Minister in writing within 90 (calendar) days after the initial decision notice is given and be accompanied by any information that you wish to have considered by the Minister. A request for reconsideration given to the Minister outside the statutory 90 day reconsideration period cannot be accepted.

The Minister may either personally undertake a request for reconsideration of an initial decision or delegate this function to an officer of the Department with the appropriate delegation.

Under section 60(3A) of *the Act*, the Minister (or the Minister's delegate) is not able to consider any information provided after the making of a request for reconsideration of an initial decision unless the information is provided in response to a request from the Minister (or the Minister's delegate), or it is information that indicates that the quality, safety or efficacy of the relevant therapeutic goods is unacceptable.

Guidelines for requesting reconsideration of an initial decision

Prior to requesting reconsideration of an initial decision, persons affected by an initial decision are advised to refer to the TGA website <https://www.tga.gov.au/reconsideration-reviewable-initial-decisions> for specific information and detailed guidance for making a request for reconsideration. A request for reconsideration should then be made in writing, signed and dated by the person requesting reconsideration and should include the following:

- a copy of the initial decision notification letter, i.e. this letter (or other evidence of notification);
- identify, and describe with as much specificity as possible, which component(s) of the initial decision should be reconsidered and set out the reasons why reconsideration is requested;
- any information/documentation in support of the request, clearly labelled to correspond with (any or each of) the reasons why reconsideration is requested; and
- an email address nominated for the purposes of receiving correspondence in relation to the request for reconsideration.

All requests for reconsideration should be given to the Minister by email:

Email: 'decision.review@health.gov.au'

Subject: "**<insert name of person/company making request> - Request for Reconsideration Under Section 60 of the *Therapeutic Goods Act 1989***"

Requests for reconsideration that include material which cannot be attached to a single email, may be submitted under multiple, sequentially numbered emails (e.g. "… - Email 1 of 3", "… - Email 2 of 3" etc). All sequentially numbered emails must be given to the Minister on the same date.

Under section 60 of *the Act*, the decision upon reconsideration by the Minister (or the Minister's delegate) must be to either 'confirm', 'revoke' or 'revoke and substitute' the initial decision. The Minister (or the Minister's delegate) must give notice in writing of the outcome of the decision upon reconsideration to the person whose interests are affected, within 60 (calendar) days after making a request for reconsideration. If the Minister (or the Minister's delegate) fails to give such notice within 60 days, the Minister (or the Minister's delegate) is deemed to have confirmed the initial decision.

Subject to the *Administrative Appeals Tribunal Act 1975* (AAT Act), if you are dissatisfied with the decision upon reconsideration by the Minister (or the Minister's delegate), you can apply to the Administrative Appeals Tribunal (AAT) for a review of that decision upon reconsideration.

NOTE: This initial decision remains in effect unless and until it is revoked or revoked and substituted by the Minister (or the Minister's delegate) as a result of a request for reconsideration under section 60 of *the Act* OR is set aside, varied or remitted by the AAT or is otherwise overturned or stayed.

Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Evaluation of s.23 New Formulation

Pharmaceutical Chemistry Variation Section
Scientific Evaluation Branch

File Number: 2012/021274
Submission Number: PM-2023-05323-1-1
eData Number: e003296 (0014-) - Cover letter

Aspen Pharmacare Australia Pty Ltd
Email: s22 @aspenpharmacare.com.au

Attention: s22 s47

Letter date: 10 November 2023

Evaluator: s22
s22

Introduction

Aspen Pharmacare Australia Pty Ltd has applied for a variation of formulation to register the following product(s):

53323 - ZANTAC ranitidine 300mg (as hydrochloride) tablet blister pack
427731 - ZANTAC ranitidine 150mg (as hydrochloride) tablet blister pack

which, while a separate and distinct good under subsection 16(1) of the Act, is the same as the currently registered medicine(s)

53323 - Suspended from ARTG - ZANTAC ranitidine 300mg (as hydrochloride) tablet blister pack

53324 - Suspended from ARTG - ZANTAC ranitidine 150mg (as hydrochloride) tablet blister pack

Aspen Pharmacare Australia Pty Ltd has also applied to make the following changes:

- Changes to the drug product formulation – including addition of croscarmellose sodium to the 150 mg strength, and changes to the type and quantity of Opadry II white (both 150 mg and 300 mg strengths). Consequential changes including:
- Addition of the following alternative drug substance site of manufacture supported by CEP s47):

  s47

  s47 (Steps: ACT)
- Changes to the drug substance specification – including test for NMDA.
- Addition of the following alternative drug product site of manufacture:

  s47

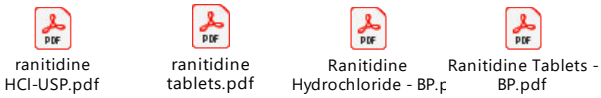
  Steps: MDD, MXP, MXR, QUAL, TCC and TMM
- Cessation of the following sites of manufacture:

  s47

  (Steps: MDD, QUAL, MXP, MXR)
- Changes to the drug product manufacture – addition of alternative batch size for bulk granule s47
- Changes to the drug product specifications – including new in-house UPLC method for related substances.
- Reduction of the drug product shelf-life to 24 months, below 25°C'.
- Changes to product labels, PI and CMI – including information about the change in tablet appearance, storage conditions, and new formulation.

An assurance that no other changes have been made to the products has been provided.

There are drug substance and/or drug product monographs in the BP, Ph. Eur., or USP, embedded below:



Evaluation

Background

Ranitidine is a common prescription and over-the-counter medicine used to treat gastric acid related conditions such as duodenal and gastric ulcers. The above listed ZANTAC ranitidine drug products were suspended from the Australian market (ARTG) in April 2020. This was due to the detection of *N*-nitrosodimethylamine (NDMA) impurity at levels above the acceptable daily intake limit of 0.32 ppm (or 0.096 µg) for ranitidine over shelf-life.

Global concern for carcinogenic risk associated with nitrosamine impurities like NDMA in drug products led to a Class II product recall by the TGA for multiple ranitidine products including the Aspen ZANTAC ranitidine products. The affected Aspen products were marketed in multiple dosage forms including tablets, effervescent, oral liquid and injection. The subsequent TGA suspension of all ZANTAC rantidine and other rantidine products was supported by a decision by the EDQM to suspend CEPs for ranitidine drug substance held by the registered manufacturers.

Following subsequent global investigation/studies headed by the US FDA, EMA, and scientific literature review into the carcinogenic risk of ranitidine derived NDMA, the sponsor has provided relevant supporting data to develop improved drug substance and drug product manufacturing standard processes to meet international acceptable limits for NMDA in their ranitidine tablet products.

Following consultation with the TGA (D23-4275817), the sponsor has now requested revocation of the suspension under paragraph. 29F(2)(a) of *the Act* and for the TGA to reinstate the above listed ZACTAC ranitidine reformulated products on the ARTG.

In addition to quality aspects of the reformulated products with respect to NDMA, key concerns raised by the TGA which were addressed by the sponsor (e003296 (0014-) - Summary of Clinical Safety) include:

In vivo formation of NDMA from ranitidine: the sponsor has presented results from four separate clinical studies conducted after the recall of ranitidine products, which investigated the metabolism and potential *in vivo* conversion of ranitidine to NDMA.

FLORIAN	JAMA Open	Effect of Oral Ranitidine on Urinary Excretion of N-Nitrosodimethylamine (NDMA)A Randomized Clinical Trial	Jun-21
GAO	JAMA Open	In Vitro Analysis of N-Nitrosodimethylamine (NDMA) Formation From Ranitidine Under Simulated Gastrointestinal Conditions	May-21
HARMON	Journal of Pharmaceutical Sciences	Ranitidine: A Proposed Mechanistic Rationale for NDMA Formation and a Potential Control Strategy	Nov-22
HARMON	Journal of Pharmaceutical Sciences	Trace aldehydes in solid oral dosage forms as catalysts for nitrosating secondary amines	Nov-22

Results from these studies did not support the *in vivo* conversion of ranitidine to NDMA in healthy population. **Resolved**.

- Link between ranitidine and cancer: It is noted from independent investigation conducted by USFDA, EMA and GSK (innovator of ranitidine products), that there is no causal link between ranitidine therapy and the development of all forms of cancer. It is noted that levels of NDMA in ranitidine are similar to those in common food products like meats. **Acceptable**.

Data in support of the quality of the reformulated products are discussed below:

Changes to DP formulations – DFNA – plus consequential changes

Note, the proposed changes to the formulations of both 150 mg and 300 mg strengths ZANTAC products were requested under the DFNA variation code, with both applications initially processed with new AUST R numbers.

However, as shown in the summary of formulation changes below, only the 150 mg strength tablet requires a new AUST R due to the addition of croscarmellose sodium (Grouping Order does not apply). Whereas the 300 mg strength should retain the original AUST R number given Grouping Order does apply to its formulation changes proposed – which should have been submitted under the DFCF code. The AET has now reassigned the original AUST R number for the 300 mg strength (D24-141546).

Table: Formulation Comparison_150mg ranitidine tablets

	Quantity per tablet	
	Proposed	Current
Ranitidine HCl	168.00mg (150mg ranitidine)	168.00mg (150mg ranitidine)
Microcrystalline cellulose	s47 [redacted]	
Croscarmellose sodium		
Magnesium stearate		
Purified water		
Opadry II white YS-22-18096		
Opadry II white YS-S-7322		

Table: Formulation Comparison_300mg ranitidine tablets

	Quantity per tablet	
	Proposed	Current
Ranitidine HCl	336.00mg (300mg ranitidine)	336.00mg (300mg ranitidine)
Microcrystalline cellulose	s47 [redacted]	
Croscarmellose sodium		
Magnesium stearate		
Purified water		
Opadry II white YS-22-18096		
Opadry II white YS-S-7322		

As shown in the above tables, the current formulations are different for each strength of the drug products. The key difference in the current formulations is that there is no croscarmellose sodium in the 150 mg strength. Now the sponsor has added croscarmellose sodium to the reformulated 150 mg product. In both proposed reformulated products, a new grade of Opadry II white (YS-22-18096) colouring agent is used to replace the current grade (YS-S-7322. The proposed Opadry II grade in listed in the Ingredients Repository (tga.gov.au). However, there is

a 9.30 mg reduction in Opadry II content of the reformulated 300 mg product in comparison to the current formulation. This was compensated for by a slight increase in the quantity of each of the other excipients in the reformulated 300 mg product. Though the addition of croscarmellose to the 150 mg reformulated product is considered a significant change that should require supporting bioequivalent data, the new 150 mg formulation is essentially a direct scale down of the 300 mg strength reformulation. Both formulations are prepared from the same bulk granule.

Given only minor change to the existing quantity of excipients (and replacement of colouring agents) are proposed in the 300 mg strength product, no bioequivalence data is required. Consequently, bioequivalence established for the current 300 mg strength formulation can be extended to the proposed 150 mg and 300 mg reformulated products (same formulation, direct scale down). Hence, dissolution data is sufficient to support the proposed changes.

Signed copies of declarations 9B - Cover letter (#36) and TSE/BSE - Excipients of Human or Animal Origin are provided in the dossier. Acceptable.

New DPM, s47

s47 is the currently registered drug product manufacturer for the suspended ranitidine products on the ARTG. The sponsor has proposed to register s47 as an alternative DPM. The proposed drug product site, s47, has a valid GMP clearance, and the site details are up to date in PARs:

Manufacturer Name:	s47
Manufacturer Address:	
Licence / Clearance Id:	MI-2023-CL-09737-1
Expiry Date:	24/08/2026
Status:	Active
Conditions:	
Location Function Code:	RA9
Manufacturing Steps:	Manufacture of dosage form Packaging and labelling Quality Control Release for supply Testing chemical and physical Testing microbial

3.2.P.3 - Manufacturing Process

It is noted that there are no changes to the registered drug product manufacturing process – which involves sifting, blending, lubrication and compression. However, a new bulk granule batch size of s47 is proposed for both strengths of the drug product. Acceptable given this is well within the currently registered maximum batch size of s47. Also process validation study was carried out on the proposed s47 bulk granule batch size. The process validation report is discussed below.

Strength	Current bulk granule batch size	Proposed, additional, bulk granule batch size
150mg	s47	
300mg		

3.2.P.3.2 - Batch Formula

The batch formula document provided has been updated accordingly to reflect the proposed formulation changes for both the current s47 and the proposed s47 batch sizes. As shown

in the above tables, the quantity of ranitidine drug substance in each reformulated product strength is the same as in the current formulation. The revised batch formula document contains the relevant DP manufacturing plan/information applicable at the proposed Stride Pharma site. The document contains a tabulated list of raw materials, suppliers, and special instructions and precautions taken before and during manufacturing process. used in the manufacturing process. Detailed manufacturing process description and schematic representation are also included in the batch formula document for each product strength. The DP shelf-life in the batch formula is 36 months – consistent with the current shelf-life.

Current and new excipients specifications provided in module 3.2.P.4 have been reviewed and considered acceptable.

3.2.P.3.5 - Process Validation

The manufacture of the reformulated products at the proposed Strides Pharma site was appropriately validated by the manufacture of three stability batches of each strength (150 mg and 300 mg) of the drug product. The batches were manufactured only on the proposed s47 batch size, none on the current s47 maximum batch size. This is acceptable. However, given only the proposed s47 batch size was validated, manufacture of the DP at the proposed s47 site is acceptable only for the s47 batch size, not for the s47 batch size. **Ask sponsor to revise the proposed batch formula**.

The quality of the manufacturing process was assessed at each critical stage and in consideration of product sensitive factors such as light and moisture. Results at each manufacturing stage were satisfactory and there were no deviations from the established process performance parameters. All manufactured stability batches comply with specified acceptance criteria. The results demonstrate that the proposed DPM, s47, can consistently and reliably produce high quality drug products, on the proposed s47 batch size, which meet the specified acceptance criteria.

Note, the quality of the drug substance used in the process validation study will be later discussed in this report.

3.2.P.5 - Drug Product Specification

The current and proposed specifications for the above listed ranitidine products are developed based on BP monograph for ranitidine tablets. A revised DP specification at release and shelf-life applied at the proposed s47 site is provided for each strength of the DP. Note, current DP specification applied at s47 is provided in sequence e003296 (0011-). Summary of changes (#15) between current and proposed specifications include:

- Addition of release (NMT s47) and expiry (NMT 0.32 ppm) limits for NDMA. The NDMA impurity is controlled in the current release and expiry specifications at NMT 0.32 ppm. Hence a tighter release limit is now proposed. The difference from release to expiry to be confirmed from stability data (see below).
- Replacement of the current HPLC method for related substances with a new in-house UPLC method. In the current DP specifications, individual primary and secondary specified impurities are controlled at NMT 0.5% and NMT 0.3% respectively, and total impurities limit is NMT 1.0% at release and NMT 1.2% at expiry. A wider total impurity limit of NMT 2.0% is proposed in the revised released and expiry specifications. Individual specified impurities in the proposed Strides Pharma specifications are referred to as Impurities C, D, E and H, with each controlled at a limit of NMT 0.3% at release and expiry. But impurities C, D, E and H are controlled at NMT 0.2 ppm in the BP

monograph. **Ask sponsor to tighten total and individual specified impurities limits in line with BP**.

- Addition of two new in-house identification tests for ranitidine hydrochloride by TLC analyses (Test B) and by silver nitrate test for chlorides. The current IR and HPLC identification tests are also retained. However, the IR test not included in the proposed specifications. **Clarify with sponsor**.
- Deletion of disintegration test (NMT 30 mins)
- Tablets descriptions updated to remove the "RAN" in the current tablet descriptions, "RAN 150" and "RAN 300", debossed on one side with on one side. The proposed debossing "150" and "300":

Product	Current	Proposed
150mg	White, film coated, biconvex tablet, engraved on one side with "RAN 150" and plain on the other	White, film coated, round tablet, engraved on one side with "150" and plain on the other
300mg	White, film coated, biconvex tablet, engraved on one side with "RAN 300" and plain on the other	White, film coated, round tablet, engraved on one side with "300" and plain on the other

All other methods remained the same including test for assay, dissolution, microbial, and Uniformity of dosage units.

Note: The proposed storage conditions "Store below 25°C. Protect from light" are included in the revised DP specifications. A note is also included regarding the presence and control of Class 2 and/or 3 solvents used in the raw material/final products manufacture. Acceptable.

3.2.P.5.3- Validation of Analytical Procedures

The proposed analytical procedures document provided in module 3.2.P.5.2 is acceptable. Specifically, the in-house HPLC for assay, UPLC for related substances, and the HPLC dissolution tests for Ranitidine tablets 150 mg and 300 mg strengths, in the proposed DP specifications have been appropriately validated. The full method validation report is provided in module 3.2.P.5.3. The report also contains detailed validation study of the in-house LC-HRMS method for NDMA impurity.

- *HPLC method for assay*: The current HPLC method for determining ranitidine assay in both strengths of the drug product was validated at the proposed s47 site with respect to precision, linearity, accuracy and linearity. The validation study was consistent with as per specified acceptance criteria. No deviations reported. Acceptable.
- *UPLC method for related substances (#54)*: The newly developed in-house UPLC system (for the determination of impurities if the finished product is equipped with Symmetry Kinetex C18 column and a UV and PDA detector. The proposed methods were re-validated in accordance with ICH Q2 guidelines. Test and standard samples used in the analysis are stable for 24 h both at room temperature and when refrigerated. The system was found to have acceptable precision level with the highest %RSD for individual specified and total impurities at 0.3 and 1.8 respectively (limits: NMT 10.0 and NMT 15.0). The method produces well resolved high purity peaks for ranitidine and each specified impurities with no co-elution or interference from blank and placebo. Results from a forced degradation study under various conditions demonstrate that the proposed method is stability indicating for the intended related substances analyses.

No cross-validation study against current in-house HPLC method or BP monograph for ranitidine tablets was carried out. However, spiked samples were used in the method validation study and the results demonstrate the proposed method satisfied the relevant acceptance criteria for all specified impurities as per current BP monograph and the proposed specifications. Though the proposed UPLC method appears to be superior to the current HPLC method for related substance, **the sponsor will be asked to provide cross-validation data against current in house HPLC and EP monograph (preferred) methods**.

LOQ and LOD for each specified impurity are below:

Name	%	
	LOD	LOQ
Ranitidine Impurity D	0.011	0.032
Ranitidine Impurity C	0.007	0.020
Ranitidine Impurity E	0.007	0.020
Ranitidine Impurity H	0.007	0.020
Ranitidine	0.007	0.020

%-Respect to sample concentration

Note: current BP monograph HPLC test method for related substances has limits of NMT 0.5% (Impurity A), NMT 0.2% (Any Secondary Single Impurity) and NMT 1.0% (Sum of secondary impurities).

- *Dissolution method*: The registered UV-Vis dissolution method was validated at the proposed site on both strengths of the DP. No discrepancies observed in the method transfer process.
- *Test for NDMA (#124)* impurity in the final drug product is carried out LC-HRMS. The proposed method validation report has been evaluated and considered satisfactory for the determination of NDMA impurity in the DP. A linear response was observed for the detection of NMDA content from 0.9 ng/mL (LOQ) to 100 ng/mL. Note, standard and test samples are prepared and kept at ca. 5°C. This test is in line with the method recommended by the FDA for assessing NDMA content in ranitidine samples (see page 51 in e003296 (0014-) - Regional Information).

3.2.P.5.4 - Batch Analyses:

CoA is provided for three batches of each strength of the drug product manufactured at the proposed s47 site using ranitidine drug substance sourced from the new supplier, s47 The batches were manufactured on the proposed s47 batch size. Batches for both DP strengths consistently comply with the proposed DP specification limits. Maximum total impurities of 0.067% and 0.07% were observed in the 150 mg and 300 mg batches respectively (limit NMT 2.0%) by the UPLC method. Individual specified impurities are reported as mostly BDL. Similarly, levels of NDMA were s4 (LOD = s47 ; limit NMT 0.32 ppm).

Comparative dissolution profile (#114) data in support of the proposed reformulated products is provided in the process validation report. Given that both 150 mg and 300 mg strengths reformulated ZANTAC products are manufactured from the same bulk granules, comparative dissolution study was carried out on only the 300 mg strength, which is considered the worst case scenario.

The dissolution study was carried out using the same registered USP Paddle method in QC media (900 mL water, 50 rpm, 45 min). Ranitidine hydrochloride is freely soluble in water and highly soluble at 37°C across the pH range pH 1 – 7.4. It is noted that due to the product recall/suspension imposed by the TGA, only expired current ZANTAC tablets were used as reference materials in the dissolution study. However, it was indicated that the expired materials (worst case scenario) were of satisfactory purity for the analyses. **Request CoA from sponsor**.

Dissolution profile study was carried out between two expired reference batches (AJF7002A and AJF9004) and the same three batches of the DP (7710129A, 7710130A and 7710131A) manufactured at the proposed Strides site using drug substance from the proposed Solara site. At least 95% of the drug substance is dissolved within 45 minutes (Q = 85% in 45 min).

Ranitidine Tablets 300mg								
B. No	RLD 1 (B.No:AJF7002A) Data from expired samples in parallel with test samples		Test 1 (http://B.No:7710129)		Test 2 (http://B.No:7710130)		Test 3 (http://B.No:7710131)	
Time point	Average	RSD	Average	RSD	Average	RSD	Average	RSD
10mins	44.8	1.9	58	8.2	58	8.6	56	4.6
15mins	83.3	1.8	74	7.4	74	3.6	70	3.8
30mins	90.8	1.1	87	7.1	86	2.0	88	6.2
45mins	98.3	0.7	95	2.7	98	3.9	95	3.5
60mins	100.9	0.9	97	2.0	103	3.0	97	3.9
F2	--		55.4		56.0		53.4	

The f_2 similarity factors calculated by the DPM between test and reference materials were >50 for all tested batches (53.4 – 63.6).

In addition, dissolution results from the same three post-variation batches were compared to results acquired from three pre-variation batches in 2016. Though pre- and post-variation data were not acquired on the same day, the results are still comparable with acceptable similarity values.

Ranitidine Tablets 300mg								
B. No	From GSK (B.No:C754) Data sourced from 2016 site transfer		Test 1 (http://B.No:7710129)		Test 2 (http://B.No:7710130)		Test 3 (http://B.No:7710131)	
Time point	Average	RSD	Average	RSD	Average	RSD	Average	RSD
10mins	68	8.7	58	8.2	58	8.6	56	4.6
15mins	78	4.1	74	7.4	74	3.6	70	3.8
30mins	91	1.9	87	7.1	86	2.0	88	6.2
45mins	96	1.6	95	2.7	98	3.9	95	3.5
60mins	101	1.2	97	2.0	103	3.0	97	3.9
F2	--		64.2		63.1		59.8	

Both comparative dissolution results demonstrate the drug product manufactured at the proposed s47 site with drug substance sourced from the proposed s47 site is comparable to the registered reference products. Given no significant changes were made to the reformulated 300 mg product, bioequivalent established for pre-variation drug products can be extended to drug products manufactured at the proposed s47 site. Though changes were made to the reformulated 150 mg strength product, its new formulation is essentially a direct scale down of the 300 mg strength. Consequently, the established bioequivalence can equally be extended to the reformulated 150 mg product.

[redacted]

[redacted]

3.2.P.8 - DP Shelf-life (Stability Data):
The current shelf-life of the suspended ZANTAC ranitidine products is 3 years when stored below 30°C. The sponsor is now proposing to reduce the shelf-life and storage conditions of the reformulated products to '24 months when stored below 25°C'. Long-term stability data in support of the proposed shelf-life was acquired at 25°C/60% RH for the same three batches of each DP strength discussed above. Up to 18 months of data is provided from the ongoing stability study. However, no accelerated stability data was provided. **Request from sponsor**.

150 mg strength batches (7710087A, 7710088A and 7710089A): All three batches comply with the proposed DP specification limits. s47 [redacted]

Each of the four specified impurities was BDL over the 18 months study period, with maximum total impurity levels observed in batch 7710089A at 0.10% (limit NMT 2.0%).

300 mg strength batches (7710129A, 7710130A and 7710131A): All three batches comply with the specified DP limits. No consistent trend was observed in NDMA impurity level – s47 [redacted] Individual specified impurities were mostly BDL.

The stability data supports the proposed 24 months.

Cessation of the following DPM is noted (expired GMP clearance). PARs not updated yet:

- s47 [redacted] (Steps: MDD, QUAL, MXP, MXR)

New DSM with CEP – s47 [redacted]

Note, Saraca Laboratories Ltd is the currently registered manufacturer of ranitidine hydrochloride drug substance. The sponsor has provided assurance to cease manufacture of the

[1] Pharmacokinetics of Ranitidine Following Oral Administration With Ascending Doses and With Multiple-Fixed Doses: https://doi.org/10.1002/j.1552-4604.1985.tb02873.x

drug substance at this site following registration of the new site. GMP clearance for this site has expired (Expiry 06/04/2021). Cessation of this site is already included in this application.

The sponsor is requesting the registration of the following site for the manufacture of ranitidine hydrochloride drug substance:

Manufacturer Name:	s47
Manufacturer Address:	
Licence / Clearance Id:	MI-2019-CL-11391-1
Expiry Date:	05/07/2024
Status:	Active
Conditions:	This clearance is issued on the basis that the manufacturer must ensure Nitrosamine testing on all Active Pharmaceutical Ingredients is acceptable prior to supply to market. The commercial supply of ranitidine products is prohibited as a result of the notice of suspension issued under section 29D of the Therapeutic Goods Act 1989 until such time that the suspension ends or is revoked.
Location Function Code:	RA1
Manufacturing Steps:	Active material manufacture

The sponsor also seeks the removal of the above pre-GMP clearance conditions after the approval of this application. The manufacture of ranitidine at the proposed s47 site is supported by a recently reinstated CEP version R1-CEP s47 that was evaluated by the EDQM. This update replaces the preceding version Rev s 4 7 which was suspended by the EDQM due to global concern of the risk associated with NDMA impurity in the drug substance.

A copy of the proposed version of the CEP is provided in module 3.2.R - cep as well as the Letters of access and relevant module 1.6 declarations. This version of the CEP was issued on s47 and is the most recent valid certificate on the EDQM database (checked on 25/01/2024). It follows current Ph. Eur. monograph for ranitidine hydrochloride plus the following supplementary tests:

- Test for the following impurities by LC-MS (Annex 2)
  - *N*-Nitrosodimethylamine (NDMA), NMT s47
- Test for the residual solvents by GC (Annex 3)
  - Isopropanol, NMT 3000 ppm
- Test for bulk and tapped density (Annex 4)
  - Tapped density, NMT 0.60 g/mL
- Test for PSD by sieve analysis: Form II (DC grade, Annex 5)
  - > 500 µm (NMT 2.0%/wt)
  - > 250 µm (NMT 50.0%/wt)
  - < 90 µm (NMT 20.0%/wt)

Re-test period of the drug substance is 24 months when stored at 2 – 8°C under nitrogen atmosphere in double polyethylene bags with silica gel and placed in polyethylene drum.

Comparison between synthetic routes applied at the current s47 site and the proposed s47 CEP process are provided in e003296 (0014-) - Cover letter (#23). Based on the proposed CEP synthetic route, and the structure of ranitidine HCl and its derivative/impurities, only NDMA was identified as a potential nitrosamine impurity in the final drug substance – with the dimethylamine group adjacent to the furan ring being the only source of NDMA.

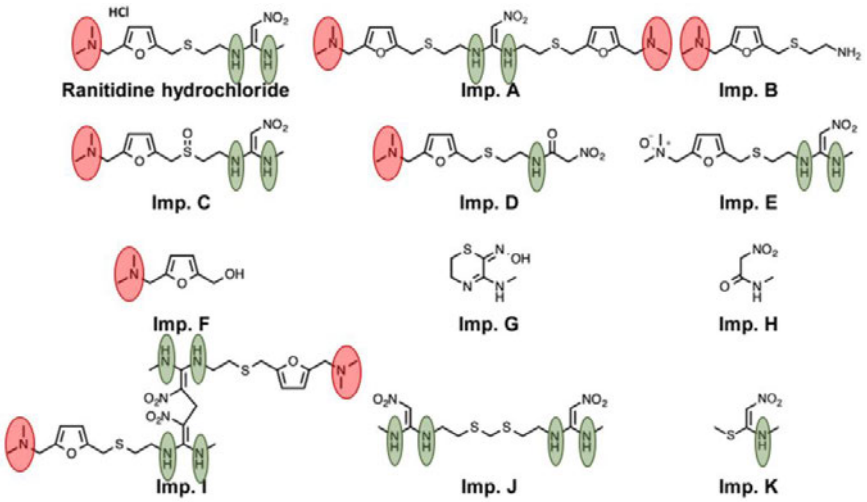


Figure 1. Possible (red) and improbable (green) sites of nitrosamine formation in drug substance and Ph. Eur. Impurities.

Quality Risk Assessment was performed by the s47 for determining NMDA content in the CEP-grade Ranitidine Hydrochloride Form II drug substance manufactured at their proposed site. The LC-HRMS method used for the analyses is consistent with the basic principles recommended by the FDA. The method uses identical LOD (0.011 ppm), LOQ (0.033 ppm) and range (0.033 – 3.33 ppm) as the FDA. The analyses show no NDMA was detected in key starting materials. It should be noted that the current s47 was the supplier of the key starting materials tested.

NDMA content in the manufacture of both the free base and the hydrochloride salt of ranitidine in fresh and recovered solvents was also investigated. No NDMA was detected in the base form produced with both fresh and recovered solvents, whereas traces of NDMA of up to 0.0044 ppm and 0.0286 ppm of NDMA were detected in the hydrochloride form manufactured with fresh and recovered solvents respectively. The results are still well within the acceptable limits of NMT 0.32 ppm.

Other parameters investigated to establish the quality control measures in the manufacturing process with respect to NDMA include the quality of water, nitrite content, formation of NDMA under stressed conditions and from equipment, packaging and transportation. Overall, the risk assessment supports the manufacturer's ability to consistently produce high quality ranitidine hydrochloride drug substance with NDMA content well within the specified NMT 0.32 ppm limit.

Manufacturer information in module 3.2.S.2 is updated correctly.

3.2.S.4 – Control of Drug Substance:
The proposed ranitidine hydrochloride drug substance specification applied at the s47 site contains all EP monograph tests/limit plus the CEP tests. Sieving analysis tests/limits from the proposed CEP is not included in the DSM specification. Though EP monograph impurities J and I are not formed in the proposed s47 CEP process, they are still included in the specification.

Tests/limits for residual solvents which are reported to be below the 30% threshold in the CEP are also listed. Limit for NDMA is consistent at NMT 0.32 ppm (release at NMT s47).

DS specification applied at the receiving DPM s47 is consistent with that applied at the DSM, plus the CEP sieving test/limits. Analytical Procedures document is also provided along with appropriate method validation report compiled by the DPM. All listed compendia methods were verified appropriately. Validation of in house methods including UPLC for related substances, LC-MS for NDMA, and the GC for residual solvents, have been reviewed and considered acceptable.

Batch Analyses data provided for three batches of the drug substance manufactured as per CEP process by s47 comply with the proposed specifications and are consistently well within the specified limits. Levels of NDMA, individual specified impurities and residual solvents were reported BDL. CoA provided by the DPM for the same batches were analysed by the Comparative impurity profile (#7) consistently show slightly higher quality of the drug substance manufactured at the proposed s47 site than batches obtained from the current s47 site – total impurities content for the three batches from current site was at 0.18 – 0.25% vs 0.03 – 0.07% for batches from s47 (limit NMT 0.5%). Comparable results were also obtained between batch analyses performed by DSM and DPM for NDMA content in batches manufactured at the proposed s47 site (BDL in all batches) e003296 (0014-) - Cover letter (#8). Comparable PSD data between current and proposed DSM batches are tabulated below:

Particle size by Malvern	Limits	SARACA RH0720150884	SARACA RH092151222	SARACA RH1020151367	SOLARA CRDE190009	SOLARA CRDE190010
D (20)	Below 150 µm	20.00µm	11.87µm	22.91 µm	28µm	62µm
D (50)	Below 210 µm	74.58µm	94.14µm	90.33 µm	181µm	163µm
D (90)	Below 355 µm	231.20µm	244.94 µm	260.62µm	338µm	295µm

3.2.S.7 - Stability Data

Accelerated (25°C / 60% RH, 6 months) and long-term stability (at 5°C for 36 months) data is provided for three recent batches of the drug substance manufactured at the proposed s47 site. Levels of NDMA and individual specified impurities remained unchanged at BDL over the 6 months of accelerated stability study. – with total impurities levels consistently at NMT 0.05% (limit NMT 0.5%). Similar results (no change) are obtained under long-term stability study over the 36 months test period. In comparison to batches manufactured at the current s47 site provided in e003296 (0014-) - stability-data (#3), both accelerated and long-term stability results from batches from the new s47 are slightly better than those from the current site. It should be noted however that the batches from the current site were tested under harsher accelerated (40°C / 75% RH) and long-term (30°C / 65% RH) storage conditions.

But the results still support the 24 months CEP retest period. Acceptable. Container-closure-system information provided in module 3.2.S.6 is consistent with CEP.

Consequential change to DP labels, PI and CMI

The changes on the proposed labels include addition of "New Formulation" and "New tablet appearance" on the main label to reflect the proposed changes.

The proposed labels are at e003296 (0014-) - Label mock-ups and specimens – clean

The labels do not meet TGO 91. **Pictogram on main label unacceptable**.

The annotated and clean copies of the proposed PI are provided in docx format. Precautionary statement "protect from heat" should be included in Section 6.4.

s.23 Evaluation Recommendation

I have considered relevant guidance in the Cat 3 Workflow Guide D19-5405621 and Standard Words D19-5649605, as applicable.

The conditions and data requirements outlined under Appendix 1 of the Minor Variations Guidance for the changes above have been provided and appropriately justified by the sponsor.

Approval of the proposed changes **is not** recommended with respect to chemistry and quality control until the above issues have been resolved.

30 January 2024

1st s.31 Response

Questions:

1. Regarding the proposed drug product specifications:
    a. It is noted in the summary of changes provided in the cover letter that both current identification tests by NIR and HPLC will be retained, in addition to the proposed TLC and chloride test methods. However, the NIR test method was not included in the drug product specifications provided for both strengths. Please clarify this and if necessary, revise the specifications as appropriate.
    b. The proposed limits for total impurities (NMT 2.0%) and specified Impurities C, D, E and H (each at NMT 0.3%) determined by the proposed UPLC method are higher than the current BP monograph limits for total impurities (NMT 1.0%) and any single secondary impurities (NMT 0.2%). Please tighten the proposed limits for total and individual specified impurities (C, D, E and H) in line with current BP monograph and provide revised specifications and supporting documents as appropriate.
    c. Please provide appropriate cross-validation data that demonstrates the proposed in-house UPLC method for related substances is superior or at least equivalent to the test method described in the current BP monograph for ranitidine tablets.

       A cross-validation data may be acquired in accordance with ICH Q1 between the proposed UPLC and the current BP monograph methods (or current in-house HPLC method) or by comparative batch analyses between the two methods on at least three **aged batches** of the drug product.
2. Given the drug product manufacturing process at the proposed s47 site was validated only for the proposed s47 batch size, and NOT for the current s47 maximum batch size, manufacture of commercial batches of the drug product intended for supply in Australia can only be carried out on the validated s47 batch size. Please update the proposed batch formula document by deleting the current s47 batch size.
3. It is noted that only expired ranitidine drug products were used as reference materials in the comparative dissolution profile data provided. Please provide for review recent certificate of analyses for the expired ranitidine reference materials to ensure the materials are still of acceptable quality.
4. Regarding the proposed drug product shelf-life:
    a. Both 18 and 24 months shelf-lives are proposed in the cover letter. Please clarify which of these two is correct and provide the relevant Module 3.2.P.8.1 Stability summary and Module 3.2.P.8.2 Post-Approval Stability Protocol/Commitment documents to reflect the proposed shelf-life.

       Given the history of the product and the fact that only 18 months of long-term stability data was provided, it is recommended that the proposed shelf-life reflects the current available 18 months stability data.

b. Please provide for review 0 to 6 months of stability data for each strength of the drug product stored under accelerated storage conditions in accordance with ICH guidelines.

5. The black square with red graphic on the main label depicting the target organ (stomach) for the drug product is considered **unacceptable** as it has potential implications for promotional aspects with regards to suggested efficacy. This is in accordance with TGA interpretation of Therapeutic Goods (Therapeutic Goods Advertising Code) Instrument 2021.

   Please revise the proposed labels (for products AUST 53323 and 53324) by deleting the graphic. Please also provide annotated copies of the current labels.

6. Please update Section 6.4 of the PI to include the precautionary statement "Protect from heat" (or "light", as appropriate).

Additional questions below:

Dear s22

As we discussed earlier on the phone, please tighten the release limit for NDMA impurity in the specifications of both strengths of the drug product.

From the 18 months long-term stability data provided, the maximum observed increase in NDMA level was at the s47 ppm for the 150 mg strength and s47 ppm for the 300 mg strength products. Please ensure that any proposed release limit for NDMA (for instance, s47) allows for the maximum observed increase over the proposed shelf-life – i.e., if the release limit is s47 , then the allowable increase from release to expiry is s47

With regards to the PI, you have also included other ZANTAC ranitidine products in dosage forms including effervescent tablets, syrup and injection. However, these additional ZANTAC products are still suspended indefinitely from the ARTG and are not included in this application. As such, please update the PI by deleting these additional products (and any specific reference, as appropriate). These products can be added to the PI at a later stage when they are reinstated to the ARTG.

To ensure the quality aspect of the PI is maintained, please note that the revised PI will be referred for clinical evaluation and further questions may arise.

Please address the above queries in your s31 response.

The above questions were raised (see D24-373283 and D24-387698).

The response to the questions raised can be found here: e003296 (0016-) - Response to request for information

Question(s):

Q1: DP specifications

a. Sponsor clarified that they NIR test for ID will be removed from the specification. **Resolved**.

b. Limits for total and specified impurities C, D, E, and H updated (tightened) in line with current BP monograph. **Resolved**.

c. No cross validation data provided initially. See e003296 (0017-) - Response to request for information for new method equivalence data.

A method equivalent study was conducted between the proposed in-house UPLC method for related substances and the current BP monograph test method. The analysis was performed on both the 150 mg and 300 mg tablet strengths.

In addition to ranitidine hydrochloride USP and Impurity A used as standards for both test methods, Impurity J was also used as a standard for the BP method (reverse phase LC with isocratic elution). Results from the analyses of both un-spiked and spiked samples show that the proposed UPLC method is at least equivalence to the BP monograph test method with respect to precision for determining related substances in both strengths of the drug product. **Resolved**.

Q2:

- Assurance is provided that only the validated s47 batch size will be supplied in Australia. This is reflected in the revised batch formula document provided. **Resolved**.

Q3:

- No CoA provided for the expired ranitidine tablets that were used as reference materials in the comparative dissolution study. The sponsor however, indicated that the material was not expected to meet the product expiry specification.

[redacted]

Q4: **DP shelf-life**

a. Sponsor has clarified that a 24 month shelf-life is proposed for both product strengths. Additional stability data at 21 and 24 months timepoints are provided for both strengths of the drug product. All tested batches still comply with the revised DP expiry specification. See results for NDMA impurity below:

Ranitidine tablets Stability - NDMA results (ppm)

S No	Product Name	Batch No	s47 [redacted]
1	Ranitidine tablets 150mg	7710087A	
2		7710088A	
3		7710089A	
4	Ranitidine tablets 300mg	7710129A	
5		7710130A	
6		7710131A	

*Reserve sample and FD sample testing in lieu of stability sample (average result)

Maximum NDMA level at 24 months was at s47 [redacted], which is still within the permitted increase from release to expiry. The updated stability data supports the proposed 24 months shelf-life. PAR updated accordingly. **Resolved**.

b. No accelerated stability data was generated/provided. Justification for this is that real time stability data was provided and the fact that NDMA levels are known to increase at elevated temperatures. Assurance is given that the first 3 post-approval commercial batches will be placed under stability study, including under accelerated storge conditions. Acceptable. **Resolved**.

Q5: As requested, the graphic on main label was removed. **Resolved**.

Q6: PI updated as requested but will be referred to the clinical team for review.

- The sponsor has agreed to retain all indications in the PI. The most recent PI was considered acceptable from a clinical perspective D24-1012503. Clean and annotated copies of the PI provided. **Resolved**.

1st s.31 Recommendation

I have considered relevant guidance in the Cat 3 Workflow Guide D19-5405621 and Standard Words D19-5649605, as applicable.

The conditions and data requirements outlined under Appendix 1 of the Minor Variations Guidance for the changes above have been provided and appropriately justified by the sponsor.

Approval of the proposed changes **is** recommended with respect to chemistry and quality control.

15 March 2024

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710087A	A.R. No. / Date	: 40000289217 / 30-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009304
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 1 of 3	

Tests	Specifications	Results
Description	White film coated round tablet, embossed with '150' on one side and plain on the other side	White film coated round tablet, embossed with '150' on one side and plain on the other side
Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay .
Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.
Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	A white, curdy precipitate is produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.
Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	1)98%, 2)98%, 3)100%, 4)98%, 5) 101%, 6)99% Avg: 99%

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s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name : Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]	
Generic Name : Ranitidine Tablets 150 mg	
Batch No. : 7710087A	A.R. No. / Date : 40000289217 / 30-Jan-2022
Batch Size : 421052 Nos	Sample No. : 1009304
Mfg. Date : 12-2021	Product Code : 3011752
Exp. Date : 11-2024	Specification No. : 2005549/PRS/R3
Customer :	Page 2 of 3

Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	L1: 4.3
Related substances by UPLC		
i) Impurity 1 (Impurity H)	Not more than 0.3%	BDL [LOD = 0.007 %]
ii) Impurity 2 (Impurity C)	Not more than 0.3%	BDL [LOD = 0.007 %]
iii) Impurity 3 (Impurity E)	Not more than 0.3%	BDL [LOD = 0.007 %]
iv) Impurity 4 (Impurity D)	Not more than 0.3%	BDL [LOD = 0.011 %]
v) Largest single unknown impurity	Not more than 0.2%	0.036 %
vi) Total impurities	Not more than 2.0%	0.067 %
Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	
	Label claim Limit	
Assay in %	150 mg - Not less than 98.0 % and not more than 105.0 %	99.9 %
Assay in mg	150 mg - Not less than 147.0 mg and not more than 157.5 mg	149.8 mg
Microbial limits		

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s47 [redacted]

CERTIFICATE OF ANALYSIS - FINISHED PRODUCT

s47 [redacted]

Product Name : Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]	
Generic Name : Ranitidine Tablets 150 mg	
Batch No. : 7710087A	A.R. No. / Date : 40000289217 / 30-Jan-2022
Batch Size : 421052 Nos	Sample No. : 1009304
Mfg. Date : 12-2021	Product Code : 3011752
Exp. Date : 11-2024	Specification No. : 2005549/PRS/R3
Customer :	Page 3 of 3

i) Total aerobic microbial count	Not more than 1000 cfu/g	LT 10
ii) Total combined yeast & molds count	Not more than 100 cfu/g	LT 10
iii) Escherichia coli	Absent/1 g	Absent
Related Substances by LC-HRMS		
i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.3 ppm	BDL (LOD=0.11 ppm)

Conclusion: .The sample complies with above standards as per IH Specifications

Remarks : Not Applicable

Checked by : s22 [redacted]	**Approved by** s22 [redacted]
Designation : Sr.Executive-QA	**Designation** : Sr. Executive - QA
Date : 31-Jan-2022	**Date** : 31-Jan-2022

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s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710088A	A.R. No. / Date	: 40000289227 / 30-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009404
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 1 of 3	

Tests	Specifications	Results
Description	White film coated round tablet, embossed with '150' on one side and plain on the other side	White film coated round tablet, embossed with '150' on one side and plain on the other side
Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay .
Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.
Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	A white, curdy precipitate is produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.
Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	1)99%, 2)93%, 3)98%, 4)98%, 5)94%, 6)100% Avg:97%

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s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710088A	A.R. No. / Date	: 40000289227 / 30-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009404
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 2 of 3	

Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	L1: 2.4
Related substances by UPLC		
i) Impurity 1 (Impurity H)	Not more than 0.3%	BDL [LOD = 0.007 %]
ii) Impurity 2 (Impurity C)	Not more than 0.3%	BDL [LOD = 0.007 %]
iii) Impurity 3 (Impurity E)	Not more than 0.3%	BDL [LOD = 0.007 %]
iv) Impurity 4 (Impurity D)	Not more than 0.3%	BQL [LOQ = 0.032 %]
v) Largest single unknown impurity	Not more than 0.2%	0.032 %
vi) Total impurities	Not more than 2.0%	0.062 %
Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine Label claim Limit	
Assay in %	150 mg - Not less than 98.0 % and not more than 105.0 %	100.7 %
Assay in mg	150 mg - Not less than 147.0 mg and not more than 157.5 mg	151.1 mg
Related Substances by LC-HRMS		

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CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710088A	A.R. No. / Date	: 40000289227 / 30-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009404
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 3 of 3	

i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.3 ppm	s47 [redacted]
Microbial limits		
i) Total aerobic microbial count	Not more than 1000 cfu/g	LT 10
ii) Total combined yeast & molds count	Not more than 100 cfu/g	LT 10
iii) Escherichia coli	Absent/1 g	Absent

Conclusion: .The sample complies with above standards as per IH Specifications

Remarks : Not Applicable

Checked by	: s22 [redacted]	**Approved by**	: s22 [redacted]
Designation	: Sr. Executive-QA	**Designation**	: Sr. Executive - QA
Date	: 31-Jan-2022	**Date**	: 31-Jan-2022

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CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710089A	A.R. No. / Date	: 40000289234 / 31-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009639
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 1 of 3	

Tests	Specifications	Results
Description	White film coated round tablet, embossed with '150' on one side and plain on the other side	White film coated round tablet, embossed with '150' on one side and plain on the other side
Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay .
Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.
Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	A white, curdy precipitate is produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.
Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	1)103%, 2)99%, 3)96%, 4)100%, 5)96%, 6)98% Avg:99%

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REGD. OFF. : [redacted]

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710089A	A.R. No. / Date	: 40000289234 / 31-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009639
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 2 of 3	

Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	L1: 1.9
Related substances by UPLC		
i) Impurity 1 (Impurity H)	Not more than 0.3%	BDL [LOD = 0.007 %]
ii) Impurity 2 (Impurity C)	Not more than 0.3%	BDL [LOD = 0.007 %]
iii) Impurity 3 (Impurity E)	Not more than 0.3%	BDL [LOD = 0.007 %]
iv) Impurity 4 (Impurity D)	Not more than 0.3%	BQL [LOQ = 0.032 %]
v) Largest single unknown impurity	Not more than 0.2%	0.034 %
vi) Total impurities	Not more than 2.0%	0.067 %
Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	
	Label claim Limit	
Assay in %	150 mg - Not less than 98.0 % and not more than 105.0 %	101.1 %
Assay in mg	150 mg - Not less than 147.0 mg and not more than 157.5 mg	151.6 mg
Related Substances by LC-HRMS		

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s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 150 mg [14s Alu-Alu-Blister] [Aus]		
Generic Name	: Ranitidine Tablets 150 mg		
Batch No.	: 7710089A	A.R. No. / Date	: 40000289234 / 31-Jan-2022
Batch Size	: 421052 Nos	Sample No.	: 1009639
Mfg. Date	: 12-2021	Product Code	: 3011752
Exp. Date	: 11-2024	Specification No.	: 2005549/PRS/R3
Customer	:	Page 3 of 3	

i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than s47 [redacted]	s47 [redacted]
Microbial limits		
i) Total aerobic microbial count	Not more than 1000 cfu/g	LT 10
ii) Total combined yeast & molds count	Not more than 100 cfu/g	LT 10
iii) Escherichia coli	Absent/1 g	Absent

Conclusion: .The sample complies with above standards as per 1H Specifications

Remarks : Not Applicable

Checked by	: s22 [redacted]	**Approved by**	: s22 [redacted]
Designation	: Sr.Executive-QA	**Designation**	: Sr. Executive - QA
Date	: 31-Jan-2022	**Date**	: 31-Jan-2022

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s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710129A	A.R. No. / Date	: 40000289284 / 31-Jan-2022
Batch Size	: 210526 Nos	Sample No.	: 1009876
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 1 of 3	

Tests	Specifications	Results
Description	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.
Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay .
Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.
Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	A white, curdy precipitate is produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.
Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	91%, 92%, 97%, 96%, 97%, 98% AVG: 95%

GQC/024/F-06/R2

This report is printed by / Printed on s22 [redacted] / 19-Apr-2022 13:49.16

WORKS : s22 [redacted]

REGD. OFF. :

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710129A	A.R. No. / Date	: 40000289284 / 31-Jan-2022
Batch Size	: 210526 Nos	Sample No.	: 1009876
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 2 of 3	

Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	L1: 3.0
Related substances by UPLC		
i) Impurity 1 (Impurity H)	Not more than 0.3%	BDL (LOD=0.007%)
ii) Impurity 2 (Impurity C)	Not more than 0.3%	BDL (LOD=0.007%)
iii) Impurity 3 (Impurity E)	Not more than 0.3%	BDL (LOD=0.007%)
iv) Impurity 4 (Impurity D)	Not more than 0.3%	BQL (LOQ=0.032)
v) Largest single unknown impurity	Not more than 0.2%	0.0338 %
vi) Total impurities	Not more than 2.0%	0.0658 %
Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	
	Label claim Limit	
Assay in %	300 mg - Not less than 98.0 % and not more than 105.0 %	102.2 %
Assay in mg	300 mg - Not less than 294.0 mg and not more than 315.0 mg	306.7 mg
Microbial limits		

GQC/024/F-06/R2

This report is printed by / Printed on s22 [redacted] / 19-Apr-2022 13:49.18

WORKS s22 [redacted]

REGD. OFF.

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710129A	A.R. No. / Date	: 40000289284 / 31-Jan-2022
Batch Size	: 210526 Nos	Sample No.	: 1009876
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 3 of 3	

i) Total aerobic microbial count	Not more than 1000 cfu/g	LT 10
ii) Total combined yeast & molds count	Not more than 100 cfu/g	LT 10
iii) Escherichia coli	Absent/1 g	Absent
Related Substances by LC-HRMS		
i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.3 ppm	BDL (LOD=s47 [redacted]

Conclusion: The sample complies with above standards as per IH Specifications

Remarks : Not Applicable

Checked by	: s22 [redacted]	**Approved by**	: s22 [redacted]
Designation	: Executive-QA	**Designation**	: Sr. Executive - QA
Date	: 03-Feb-2022	**Date**	: 03-Feb-2022

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GQC/024/F-06/R2

This report is printed by / Printed on s22 [redacted] / 19-Apr-2022 13:49.18

WORKS : s22 [redacted]

REGD. OFF. : [redacted]

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710130A	A.R. No. / Date	: 40000289303 / 01-Feb-2022
Batch Size	: 210526 Nos	Sample No.	: 1009934
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 1 of 3	

Tests	Specifications	Results
Description	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.
Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay
Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.
Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	A white, curdy precipitate is produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.
Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	100%, 100%, 100%, 92%, 92%, 92 % AVG: 96%

This report is printed by/ Printed on : s22 [redacted] 19-Apr-2022 13:58:19

s22 [redacted]

WORKS :

REGD. OFF. :

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name : Ranitidine tablets 300mg [14s Alu-Alu Blister].[AUS]	
Generic Name : Ranitidine Tablets 300 mg	
Batch No. : 7710130A	A.R. No. / Date : 40000289303 / 01-Feb-2022
Batch Size : 210526 Nos	Sample No. : 1009934
Mfg. Date : 01-2022	Product Code : 3011771
Exp. Date : 12-2024	Specification No. : 2005550/PRS/R3
Customer :	Page 2 of 3

Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	L I: 3.0
Related substances by UPLC		
i) Impurity I (Impurity H)	Not more than 0.3%	BDL [LOD=0.007%]
ii) Impurity 2 (Impurity C)	Not more than 0.3%	BDL [LOD=0.007%]
iii) Impurity 3 (Impurity E)	Not more than 0.3%	BDL [LOD=0.007%]
iv) Impurity 4 (Impurity D)	Not more than 0.3%	BDL [LOD=0.011%]
v) Largest single unknown impurity	Not more than 0.2%	0.036 %
vi) Total impurities	Not more than 2.0%	0.07 %
Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine Label claim Limit	
Assay in %	300 mg - Not less than 98.0 % and not more than 105.0 %	102.4 %
Assay in mg	300 mg - Not less than 294.0 mg and not more than 315.0 mg	307.1 mg
Related Substances by LC-HRMS		

GQC/024/F-06/R2

This report is printed by / Printed on s22 [redacted] / 19-Apr-2022 13:58.21

WORKS : s22 [redacted]

REGD. OFF. :

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710130A	A.R. No. / Date	: 40000289303 / 01-Feb-2022
Batch Size	: 210526 Nos	Sample No.	: 1009934
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 3 of 3	

i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.3 ppm	BDL (LOD=s47 [redacted]
Microbial limits		
i) Total aerobic microbial count	Not more than 1000 cfu/g	LT 10
ii) Total combined yeast & molds count	Not more than 100 cfu/g	LT 10
iii) Escherichia coli	Absent/1 g	Absent

Conclusion: .The sample complies with above standards as per IH Specifications

Remarks : Not Applicable

Checked by	: s22 [redacted]	**Approved by**	: s22 [redacted]
Designation	: Executive-QA	**Designation**	: Sr. Executive - QA
Date	: 03-Feb-2022	**Date**	: 03-Feb-2022

Note : **This document is produced electronically and is valid without handwritten signature**

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This report is printed by / Printed on s22 [redacted] / 19-Apr-2022 13:58.21

WORKS : s22 [redacted]

REGD. OFF. : [redacted]

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710131A	A.R. No. / Date	: 40000289362 / 01-Feb-2022
Batch Size	: 210526 Nos	Sample No.	: 1010054
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 1 of 3	

Tests	Specifications	Results
Description	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.
Identification A	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay .
Identification B	By Thin layer chromatography: The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.	The Rf value of the principal spot in the sample solution corresponds to that of the standard solution.
Identification C	For Chlorides: A white, curdy precipitate to be produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.	A white, curdy precipitate is produced that is insoluble in nitric acid but is soluble in a slight excess of 6N Ammonium hydroxide.
Dissolution	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	1)98%, 2)94%, 3)95%, 4)96%, 5)92%, 6)99% Avg: 96%

GQC/024/F-06/R2

This report is printed by / Printed on s22 [redacted] 19-Apr-2022 14:12.21

WORKS s22 [redacted]

REGD.OFF.

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name : Ranitidine tablets 300mg [14s Alu-Alu Blister] [AUS]	
Generic Name : Ranitidine Tablets 300 mg	
Batch No. : 7710131A	A.R. No. / Date : 40000289362 / 01-Feb-2022
Batch Size : 210526 Nos	Sample No. : 1010054
Mfg. Date : 01-2022	Product Code : 3011771
Exp. Date : 12-2024	Specification No. : 2005550/PRS/R3
Customer :	Page 2 of 3

Uniformity of dosage units by weight variation	Acceptance value is less than or equal to 15.0	L1: 4.3
Related substances by UPLC		
i) Impurity 1 (Impurity H)	Not more than 0.3%	BDL (LOD=0.007%)
ii) Impurity 2 (Impurity C)	Not more than 0.3%	BDL (LOD=0.007%)
iii) Impurity 3 (Impurity E)	Not more than 0.3%	BDL (LOD=0.007%)
iv) Impurity 4 (Impurity D)	Not more than 0.3%	BQL (LOQ=0.032)
v) Largest single unknown impurity	Not more than 0.2%	0.037 %
vi) Total impurities	Not more than 2.0%	0.07 %
Assay by HPLC	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine Label claim Limit	
Assay in %	300 mg - Not less than 98.0 % and not more than 105.0 %	102.4 %
Assay in mg	300 mg - Not less than 294.0 mg and not more than 315.0 mg	307.2 mg
Related Substances by LC-HRMS		

GQC/024/F-06/R2

This report is printed by / Printed on s22 [redacted] / 19-Apr-2022 14:12.24

s22 [redacted]

WORKS

REGD.OF

s47 [redacted]

CERTIFICATE OF ANALYSIS : FINISHED PRODUCT

s47 [redacted]

Product Name	: Ranitidine tablets 300mg [14s Alu-Alu Blister].[AUS]		
Generic Name	: Ranitidine Tablets 300 mg		
Batch No.	: 7710131A	A.R. No. / Date	: 40000289362 / 01-Feb-2022
Batch Size	: 210526 Nos	Sample No.	: 1010054
Mfg. Date	: 01-2022	Product Code	: 3011771
Exp. Date	: 12-2024	Specification No.	: 2005550/PRS/R3
Customer	:	Page 3 of 3	

i) N-Nitrosodimethylamine (NDMA Impurity)	Not more than 0.3 ppm	BDL(LODs47 [redacted])
Microbial limits		
i) Total aerobic microbial count	Not more than 1000 cfu/g	LT 10
ii) Total combined yeast & molds count	Not more than 100 cfu/g	LT 10
iii) Escherichia coli	Absent/1 g	Absent

Conclusion: .The sample complies with above standards as per IH Specifications

Remarks: Refer change control for NDMA impurity test: TC-PYF/2022/011.

Checked by	: s22 [redacted]	**Approved by**	: s22 [redacted]
Designation	: Executive-QA	**Designation**	: Sr. Executive - QA
Date	: 03-Feb-2022	**Date**	: 03-Feb-2022

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WORKS : s22 [redacted]

REGD. OFF. :

From: eSubmissions
To: s22 [redacted]
Cc:
Subject: PM-2023-05323-1-1 - ranitidine hydrochloride - Aspen Pharmacare Australia Pty Ltd - 2nd s31 [SEC=OFFICIAL]
Date: Wednesday, 6 March 2024 12:18:57 PM
Attachments: image001.png
image002.png
0016.zip
response.pdf
Importance: High

Good Afternoon,

Please find S31 Response attached and saved to file 2012/021274. The Section 31 Response event has been completed in Premier.
The docubridge link is: e003296 - (0016)

Kind Regards,

s22 [redacted]
Administration Officer – Application Entry, Support and Export Section

Prescription Medicines Authorisation Branch | Medicines Regulation Division
Health Products Regulation Group (Therapeutic Goods Administration)
Australian Government Department of Health and Aged Care
E: s22 [redacted] @health.gov.au
Location: Fairbairn, A.C.T.
PO Box 100, Canberra ACT 2601, Australia

The Department of Health and Aged Care acknowledges First Nations peoples as the Traditional Owners of Country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to all Elders both past and present.

From: s22 [redacted] @aspenpharmacare.com.au>
Sent: Wednesday, March 6, 2024 11:05 AM
To: s22 [redacted] @Health.gov.au>; eSubmissions <eSubmissions@health.gov.au>; PCS CAT 3 S31 <PCSCAT3S31@health.gov.au>
Cc: s22 [redacted] @health.gov.au>
Subject: RE: PM-2023-05323-1-1 - ranitidine hydrochloride - Aspen Pharmacare Australia Pty Ltd - 2nd s31
Importance: High

Confidential

Good Morning s22 [redacted]
How are you?
As promissed – please find attached Aspen's full response to your S31 request – sequence 0016
I'm free most of the afternoon if you need to call me to discuss anything

Have a lovely day

Kind Regards
s22

[redacted] | s47 [redacted] |Strategic and Technical Affairs | Aspen Australia
s22 [redacted]

From: s22 [redacted] @Health.gov.au>
Sent: Wednesday, January 31, 2024 1:59 PM
To: s22 [redacted] @aspenpharmacare.com.au>
Cc: s22 [redacted] @health.gov.au>
Subject: [SEC=OFFICIAL] RE: PM-2023-05323-1-1 - ranitidine hydrochloride - Aspen Pharmacare Australia Pty Ltd - 2nd s31

Dear s22 [redacted]

As we discussed earlier on the phone, please tighten the release limit for NDMA impurity in the specifications of both strengths of the drug product.

From the 18 months long-term stability data provided, the maximum observed increase in NDMA level was at the 12 months timepoint at s47 [redacted] for the 150 mg strength and s47 [redacted] ppm for the 300 mg strength products. Please ensure that any proposed release limit for NDMA (for instance, s47 [redacted] ppm) allows for the maximum observed increase over the proposed shelf-life – i.e. if the release limit is s47 [redacted] ppm, then the allowable increase from release to expiry is s47 [redacted] ppm s47 [redacted] ppm).

With regards to the PI, you have also included other ZANTAC ranitidine products in dosage forms including effervescent tablets, syrup and injection. However, these additional ZANTAC products are still suspended indefinitely from the ARTG and are not included in this application. As such, please update the PI by deleting these additional products (and any specific reference, as appropriate). These products can be added to the PI at a later stage when they are reinstated to the ARTG.

To ensure the quality aspect of the PI is maintained, please note that the revised PI will be referred for clinical evaluation and further questions may arise.

Please address the above queries in your s31 response.

Kind Regards,

s22 [redacted]
Evaluator - Pharmaceutical Chemistry Variations Section
Scientific Evaluation Branch | Medicines Regulation Division | Health Products Regulation Group
Therapeutic Goods Administration
Australian Government Department of Health and Aged Care
s22 [redacted] @health.gov.au
Location: 160 Ann Street, Brisbane

PO Box 9848, Brisbane QLD 4001, MDP 116, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present

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From: s22 @aspenpharmacare.com.au>
Sent: Tuesday, January 30, 2024 5:46 PM
To: s22 .THOMAS@Health.gov.au>
Cc: s22 Webb@health.gov.au>
Subject: RE: PM-2023-05323-1-1 - ranitidine hydrochloride - Aspen Pharmacare Australia Pty Ltd - 2nd s31

Confidential

Good evening s 22

Thank you so much for your email and I will endevour to have a response to you as soon as practicable.

Will there be any further questions around the nitrosamines limits proposed for the finished product?

Many thanks and Kind Regards

s22

s22 | s47 |Strategic and Technical Affairs | Aspen Australia

s22

From: s22 @Health.gov.au>
Sent: Tuesday, January 30, 2024 6:41 PM
To: s22 @aspenpharmacare.com.au>
Cc: s22 @health.gov.au>
Subject: [SEC=OFFICIAL] PM-2023-05323-1-1 - ranitidine hydrochloride - Aspen Pharmacare Australia Pty Ltd - 2nd s31

Dear Sir/ Madam,

In relation to the products referred to in the submission above and in accordance with section 31 of the Act, would you please provide the required information as detailed below by: **26 February 2024**
If you believe that the time allowed is inadequate or you have difficulties meeting the due

date, please contact me as soon as possible.

INFORMATION REQUIRED

1. Regarding the proposed drug product specifications:
    a. It is noted in the summary of changes provided in the cover letter that both current identification tests by NIR and HPLC will be retained, in addition to the proposed TLC and chloride test methods. However, the NIR test method was not included in the proposed drug product specifications provided for both strengths. Please clarify this and if necessary, revise the specifications as appropriate.
    b. The proposed limits for total impurities (NMT 2.0%) and specified Impurities C, D, E and H (each at NMT 0.3%) determined by the proposed UPLC method are higher than the current BP monograph limits for total impurities (NMT 1.0%) and any single secondary impurities (NMT 0.2%). Please tighten the proposed limits for total and individual specified impurities (C, D, E and H) in line with current BP monograph and provide revised specifications and supporting documents as appropriate.
    c. Please provide appropriate cross-validation data that demonstrates the proposed in-house UPLC method for related substances is superior or at least equivalent to the test method described in the current BP monograph for ranitidine tablets.

       A cross-validation data may be acquired in accordance with ICH Q1 between the proposed UPLC and the current BP monograph methods (or current in-house HPLC method) or by comparative batch analyses between the two methods on at least three **aged batches** of the drug product.
2. Given the drug product manufacturing process at the proposed s47 [redacted] site was validated only for the proposed s47 Kg batch size, and NOT for the current 450 Kg maximum batch size, manufacture of commercial batches of the drug product intended for supply in Australia can only be carried out on the validated s47 Kg batch size. Please update the proposed batch formula document by deleting the current 450 Kg batch size.
3. It is noted that only expired ranitidine drug products were used as reference materials in the comparative dissolution profile data provided. Please provide for review recent certificate of analyses for the expired ranitidine reference materials to ensure the materials are still of acceptable quality.
4. Regarding the proposed drug product shelf-life:
    a. Both 18 and 24 months shelf-lives are proposed in the cover letter. Please clarify which of these two is correct and provide the relevant Module 3.2.P.8.1 Stability summary and Module 3.2.P.8.2 Post-Approval Stability Protocol/Commitment documents to reflect the proposed shelf-life.

       Given the history of the product and the fact that only 18 months of long-term stability data was provided, it is recommended that the proposed shelf-life reflects the current available 18 months stability data.
    b. Please provide for review 0 to 6 months of stability data for each strength of the drug product stored under accelerated storage conditions in accordance with ICH guidelines.
5. The black square with red graphic on the main label depicting the target organ (stomach) for the drug product is considered **unacceptable** as it has potential implications for promotional aspects with regards to suggested efficacy. This is in accordance with TGA interpretation of Therapeutic Goods (Therapeutic Goods Advertising Code) Instrument 2021.
   Please revise the proposed labels (for products AUST 53323 and 53324) by deleting the graphic. Please also provide annotated copies of the current labels.
6. Please update Section 6.4 of the PI to include the precautionary statement “Protect from

heat" (or "light", as appropriate).

Please ensure that the relevant parts of Modules 1 and 3 are updated (if required) to reflect your response above.

RESPONSE REQUIREMENTS

Please title your response as formatted below:
RESPONSE TO S31 REQUEST PM-2023-05323-1-1-PCE-2, FILE NUMBER 2012/021274, eSubmission identifier e003296.

Please note that failure to label your response appropriately may lead to delays in processing the submitted response. Our business rules state that if a reply is received without the s31 Request Number, TGA will not restart the "clock" until five days after receipt. This extra time is used to match the reply with the correct s31 request.

Adequate timeframe

Please make an assessment of the time involved in replying to this request and, if you believe that you need more time than that allocated above, raise your concerns with me immediately.
If you believe now that the time allowed is adequate, but at some stage in the process of documenting your reply you have difficulties meeting the due date, please contact me as soon as you are aware of those difficulties.
The time allowed for evaluation of your application will be extended by the time you take to respond fully to this request. Partial responses will not restart the "clock".

Address for reply

Your response should be sent by email to s22 [redacted] @tga.gov.au and also copy to s22 [redacted] @health.gov.au in an electronic format (eCTD) - subject to data size restrictions, and s22 [redacted] @health.gov.au.

If it is not possible to email, please send CD, DVD or USB drive to:

Postal address
S31 Response
Dossiers (PRESCRIPTION MEDICINES)
Records Management
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

Or

Courier (street address)
S31 Response Dossiers (PRESCRIPTION MEDICINES) Records Management Therapeutic Goods Administration
27 Scherger Drive,
ACT 2609
Australia

Please note that other aspects of the submission are under review and further questions may arise

Kind Regards,

s22

Evaluator - Pharmaceutical Chemistry Variations Section

Scientific Evaluation Branch | Medicines Regulation Division | Health Products Regulation Group
Therapeutic Goods Administration
Australian Government Department of Health and Aged Care
s22 @health.gov.au
Location: 160 Ann Street, Brisbane
PO Box 9848, Brisbane QLD 4001, MDP 116, Australia

The Department of Health and Aged Care acknowledges the traditional owners of country throughout Australia, and their continuing connection to land, sea and community. We pay our respects to them and their cultures, and to elders both past and present

s47

Formulation Unit II - s47

s47

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Period / Test	Appearance	Identification A [by HPLC] [IH] / Identification A	Dissolution	Related Substances by LC-HRMS i) N-Nitroso dimethylamine (NDMA Impurity)	Sample pulled on	Reference A.R No.	Date of Release
Limit	White film coated round tablet, embossed with '150' on one side and plain on the other side	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	Not more than 0.3 ppm	NA	NA	NA
Initial	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1:98%,98%,100%, 98%, 101%,99% Avg: 99%	s47	NA	40000289217	31/01/2022
03M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 98%, 93%, 95%, 104%, 97%, 98%, Avg.: 97%	s47	02/05/2022	1041972	16/07/2022
06M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 93%, 93%, 93%, 93%, 93%, 93%, Avg.:93%	s47 ppm	01/08/2022	1072913	03/12/2022

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

09M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 95%, 90%, 96%, 93%, 92%, 92%, Avg.:93%	s47 [redacted] ppm	01/11/2022	1102267	11/03/2023
12M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 88%, 89%, 92%, 92%, 80%, 95%, S2: 96%, 95%, 95%, 92%, 93%, 98%, Avg.: 92%	s47 [redacted] ppm	02/02/2023	1129884	03/05/2023
15M	NA	NA	NA	s47 [redacted] ppm	NA	NA	NA
18M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 100%, 94%, 83%, 100%, 92%, 97%, S2: 97%, 99%, 96%, 96%, 94%, 100%, Avg.: 96%	s47 [redacted] ppm	02/08/2023	1196448	12/09/2023
21M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 92%, 94%, 95%, 94%, 89%, 95% Avg.: 93%	s47 [redacted] ppm	02/11/2023	1230275	18/11/2023

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

24M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 95%, 102%, 95%, 103%, 97%, 97%, Avg.: 98%	0.22 ppm	02/02/2024	1263296	05/03/2024
ASL							
36M							

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Period / Test	Related substances by UPLC						Sample pulled on	Reference A.R No.	Date of Release
	i) Impurity 1 (Impurity H)	ii) Impurity 2 (Impurity C)	iii) Impurity 3 (Impurity E)	iv) Impurity 4 (Impurity D)	v) Largest single unknown impurity	vi) Total impurities			
Limit	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.2%	Not more than 2.0%	NA	NA	NA
Initial	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.036 %	0.067 %	NA	40000289217	31/01/2022
03M	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	02/05/2022	1041972	16/07/2022
06M	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	01/08/2022	1072913	03/12/2022
09M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	01/11/2022	1102267	11/03/2023
12M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.011%]	0.041%	0.10%	02/02/2023	1129884	03/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA	NA
18M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BDL [LOD =0.007%]	BDL [LOD = 0.011%]	0.02%	0.04%	02/08/2023	1196448	12/09/2023
21M	BDL [LOD = 0.007 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.03 %	0.03 %	02/11/2023	1230275	18/11/2023
24M	BDL [LOD = 0.007 %]	BQL [LOQ=0.020%]	BDL [LOD =0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	02/02/2024	1263296	05/03/2024

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] / 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

ASL									
36M									

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

↓ Period / Test →	Microbial limits			Assay by HPLC		Sample pulled on	Reference A.R No.	Date of Release
	i) Total aerobic microbial count	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine	iii) Escherichia coli	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine				
Limit	Not more than 1000 cfu/g	Not more than 100 cfu/g	Absent/g	150 mg - Not less than 95.0 % and not more than 105.0 %	150 mg - Not less than 142.5 mg and not more than 157.5 mg	NA	NA	NA
Initial	LT 10cfu/g	LT 10cfu/g	Absent/g	99.9%	149.8mg	NA	40000289217	31/01/2022
03M	NA	NA	NA	100.6%	151.0mg	02/05/2022	1041972	16/07/2022
06M	LT 10cfu/g	LT 10cfu/g	Absent/g	99.8%	149.7mg	01/08/2022	1072913	03/12/2022
09M	NA	NA	NA	100.4%	150.6mg	01/11/2022	1102267	11/03/2023
12M	LT 10cfu/g	LT 10cfu/g	Absent/g	98.6%	148.0mg	02/02/2023	1129884	03/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA
18M	NA	NA	NA	98.9%	148.4mg	02/08/2023	1196448	12/09/2023
21M	NA	NA	NA	100.0 %	150.0 mg	02/11/2023	1230275	18/11/2023
24M	LT 10cfu/g	LT 10cfu/g	Absent/g	102.1%	153.2mg	02/02/2024	1263296	05/03/2024
ASL								
36M								

Note: NA-Not Applicable. M-month. 15M NDMA Analysis performed from FG stock which was stored in 15°C to 25°C.

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: [redacted]	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Remarks:
Note 1: Initial to 12M results updated from 7710087A protocol no: TAB/MST/21/435/R2. 15M NDMA result updated from FG stock analysis. From 18M onwards stability incubation and analysis has been resumed as per protocol TAB/PYF/005/23/00.
Note 2: Refer OOT.No: PYF/OOT/2023/0206 18M Interval.
Note 3: PYF/DR/2024/035 for 24M.

Review Checkpoints:

1	If any OOS/OOT is recorded, investigation and disposition action is completed. (OOS/OOT reference No.:PYF/OOT/2023/0206)	☑ Yes ☒ No ☒ NA
2	If confirmed OOS/OOT, the following action (s) is recommended	
	• Change in specification limit	☒ Yes ☒ No ☑ NA
	• Shelf-life reduction	☒ Yes ☒ No ☑ NA
	• Any Other Action-(Specify if yes, add attachment if necessary)	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC or CAPA No.: - NA	
3	If any deviation is recorded, Deviation reference No.: PYF/DR/2024/035 for 24M. Remarks (if any): Nil	
4	Shelf-life extension is recommended	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC No.: - NA)	

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710087A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Conclusion: - The product **complies** / ~~**does not comply**~~ with the specification till the time stability study is conducted/ shelf life of the product.

Comment (if any): Nil

s47 [redacted]

Formulation Unit II - s47 [redacted]

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

Period / Test	Appearance	Identification A [by HPLC] [IH] / Identification A	Dissolution	Related Substances by LC-HRMS i) N-Nitroso dimethylamine (NDMA Impurity)	Sample pulled on	Reference A.R No.	Date of Release
Limit	White film coated round tablet, embossed with '150' on one side and plain on the other side	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	Not more than 0.3 ppm	NA	NA	NA
Initial	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1:99%, 93%, 98%, 98%,94%, 100% Avg:97%	BDL (LOD= s47 [redacted] ppm)	NA	40000289227	31/01/2022
03M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 102%, 96%, 96%, 95%, 101%, 102%, Avg.: 99%	BQL (LOQ= s47 [redacted] ppm)	02/05/2022	1041975	16/07/2022
06M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	.S1: 97%, 97%, 100%, 98%, 98%, 98%, Avg.:98%	s47 [redacted] ppm	01/08/2022	1072916	07/10/2022

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] / 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

09M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 97%, 97%, 95%, 97%, 90%, 95%, Avg.:95%	s47 [redacted] ppm	01/11/2022	1102269	31/01/2023
12M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 98%, 94%, 91%, 98%, 92%, 88%, Avg.:94%	s47 [redacted] ppm	02/02/2023	1129885	05/05/2023
15M	NA	NA	NA	s47 [redacted] ppm	NA	NA	NA
18M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 96%, 96%, 97%, 99%, 93%, 102%, Avg.: 97%	s47 [redacted] ppm	02/08/2023	1196449	12/09/2023
21M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 92%, 94%, 95%, 94%, 89%, 95% Avg.: 93%	s47 [redacted] ppm	02/11/2023	1230275	18/11/2023
24M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 97%, 98%, 100%, 98%, 95%, %, Avg.: 98%	0.20 ppm	03/02/2024	1263297	05/03/2024

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

36M							
ASL							

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 / 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

Period / **Test**	**Related substances by UPLC**						**Sample pulled on**	**Reference A.R No.**	**Date of Release**
	i) Impurity 1 (Impurity H)	**ii) Impurity 2 (Impurity C)**	**iii) Impurity 3 (Impurity E)**	**iv) Impurity 4 (Impurity D)**	**v) Largest single unknown impurity**	**vi) Total impurities**			
Limit	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.2%	Not more than 2.0%	NA	NA	NA
Initial	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BQL [LOQ = 0.032%]	0.032 %	0.062%	NA	40000289227	31/01/2022
03M	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	02/05/2022	1041975	16/07/2022
06M	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD=0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	01/08/2022	1072916	07/10/2022
09M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BDL [LOD=0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	01/11/2022	1102269	31/01/2023
12M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BQL [LOQ=0.020%]	BDL [LOD = 0.011%]	0.040%	0.09%	02/02/2023	1129885	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA	NA
18M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BDL [LOD=0.007%]	BDL [LOD = 0.011%]	0.02%	0.02%	02/08/2023	1196449	12/09/2023
21M	BDL [LOD = 0.007 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.03%	0.03%	01/11/2023	1230275	18/11/2023
24M	BDL [LOD=0.007%]	BQL [LOQ=0.020%]	BDL [LOD=0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	03/02/2024	1263297	05/03/2024

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] / 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

36M									

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] / 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

Period / Test	Microbial limits			Assay by HPLC		Sample pulled on	Reference A.R No.	Date of Release
	i) Total aerobic microbial count	ii) Total combined yeast & molds count	iii) Escherichia coli	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine				
Limit	Not more than 1000 cfu/g	Not more than 100 cfu/g	Absent/g	150 mg - Not less than 95.0 % and not more than 105.0 %	150 mg - Not less than 142.5 mg and not more than 157.5 mg	NA	NA	NA
Initial	LT 10cfu/g	LT 10cfu/g	Absent/g	100.7%	151.1mg	NA	40000289227	31/01/2022
03M	NA	NA	NA	101.5%	152.2mg	02/05/2022	1041975	16/07/2022
06M	LT 10cfu/g	LT 10cfu/g	Absent/g	98.8%	148.2mg	01/08/2022	1072916	07/10/2022
09M	NA	NA	NA	99.1%	148.7mg	01/11/2022	1102269	31/01/2023
12M	LT 10cfu/g	LT 10cfu/g	Absent/g	99.3%	148.9mg	02/02/2023	1129885	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA
18M	NA	NA	NA	99.9%	149.8mg	02/08/2023	1196449	12/09/2023
21M	NA	NA	NA	100.0 %	150.0 mg	01/11/2023	1230275	18/11/2023
24M	LT 10cfu/g	LT 10cfu/g	Absent/g	101.4 %	152.2mg	03/02/2024	1263297	05/03/2024
ASL								
36M								

NA-Not Applicable. M-month. 15M NDMA Analysis performed from FG stock which was stored in 15°C to 25°C.

Remarks:

Note1: Initial to 12M results updated from 7710088A protocol no: TAB/MST/21/454/R2. 15M NDMA result updated from FG stock analysis. From 18M onwards stability incubation and analysis has been resumed as per protocol TAB/PYF/005/23/00.

Note 2: Reference deviation no: PYF/DR/2024/035 for 24M

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710088A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASLand 36 months				

Review Checkpoints:

1	If any OOS/OOT is recorded, investigation and disposition action is completed (OOS/OOT reference No.: NA)	☒ Yes ☒ No ☑ NA
2	If confirmed OOS/OOT, the following action (s) is recommended	
	• Change in specification limit	☒ Yes ☒ No ☑ NA
	• Shelf-life reduction	☒ Yes ☒ No ☑ NA
	• Any Other Action-(Specify if yes, add attachment if necessary)	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC or CAPA No.: - NA	
3	If any deviation is recorded, Deviation reference No.: PYF/DR/2024/035 for 24M Remarks (if any): Nil	
4	Shelf-life extension is recommended	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC No.: - NA)	

Conclusion: - The product **complies** / ~~**does not comply**~~ with the specification till the time stability study is conducted/ shelf life of the product.

Comment (if any): Nil

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

Period / Test	Appearance	Identification A [by HPLC] [IH] / Identification A	Dissolution	Related Substances by LC-HRMS i) N-Nitroso dimethylamine (NDMA Impurity)	Sample pulled on	Reference A.R No.	Date of Release
Limit	White film coated round tablet, embossed with '150' on one side and plain on the other side	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	Not more than 0.3 ppm	NA	NA	NA
Initial	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1:103%, 99%, 96%, 100%, 96%, 98% Avg:99%	s47 [redacted]	NA	40000289234	31/01/2022
03M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 93%, 91%, 93%, 102%, 92%, 98%, Avg: 95%	s47 [redacted] ppm	02/05/2022	1041978	19/07/2022
06M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 95%, 92%, 96%, 95%, 95%, 93%, Avg.: 94%	s47 [redacted] ppm	01/08/2022	1072919	07/10/2022

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

09M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 93%, 98%, 99%, 98%, 94%, 98%, Avg.:97%	s47 [redacted] ppm	01/11/2022	1102271	01/02/2023
12M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 94%, 92%, 101%, 85%, 101%, 101%, Avg.: 96%	s47 [redacted] ppm	02/02/2023	1129888	05/05/2023
15M	NA	NA	NA	s47 [redacted] ppm	NA	NA	NA
18M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 104%, 99%, 99%, 95%, 94%, 104%, Avg.: 99%	s47 [redacted] ppm	02/08/2023	1196450	12/09/2023
21M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 96%, 95%, 93%, 92%, 93%, 95% Avg.: 94%	s4 [redacted] ppm	01/11/2023	1230278	18/11/2023
24M	White film coated round tablet, embossed with '150' on one side and plain on the other side	Complies	S1: 99%, 95%, 94%, 97%, 95%, 97% , Avg.: 96%	0.24 ppm	02/02/2024	1263298	05/03/2024
ASL							

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

36							

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

Period / Test	Related substances by UPLC						Sample pulled on	Reference A.R No.	Date of Release
	i) Impurity 1 (Impurity H)	ii) Impurity 2 (Impurity C)	iii) Impurity 3 (Impurity E)	iv) Impurity 4 (Impurity D)	v) Largest single unknown impurity	vi) Total impurities			
Limit	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.2%	Not more than 2.0%	NA	NA	NA
Initial	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BQL [LOQ = 0.032%]	0.034 %	0.067 %	NA	40000289234	31/01/2022
03M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	02/05/2022	1041978	19/07/2022
06M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	01/08/2022	1072919	07/10/2022
09M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	01/11/2022	1102271	01/02/2023
12M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.011%]	0.043 %	0.10 %	02/02/2023	1129888	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA	NA
18M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.02%	0.04%	02/08/2023	1196450	12/09/2023
21M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.03 %	0.03 %	01/11/2023	1230278	18/11/2023

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

24M	BDL [LOD = 0.007 %]	BQL(LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL (LOD=0.011%)	BQL (LOQ=0.020%)	BQL	02/02/2024	1263298	05/03/2024
ASL									
36M									

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

Period ↓ **Test** →	**Microbial limits**			**Assay by HPLC**		**Sample pulled on**	**Reference A.R No.**	**Date of Release**
	i) Total aerobic microbial count	**ii) Total combined yeast & molds count**	**iii) Escherichia coli**	**Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine**				
Limit	Not more than 1000 cfu/g	Not more than 100 cfu/g	Absent/g	150 mg - Not less than 95.0 % and not more than 105.0 %	150 mg - Not less than 142.5 mg and not more than 157.5 mg	NA	NA	NA
Initial	LT 10 cfu/g	LT 10 cfu/g	Absent/g	101.1 %	151.6 mg	NA	40000289234	31/01/2022
03M	NA	NA	NA	99.9 %	149.8 mg	02/05/2022	1041978	19/07/2022
06M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	101.7 %	152.5 mg	01/08/2022	1072919	07/10/2022
09M	NA	NA	NA	100.4 %	150.7 mg	01/11/2022	1102271	01/02/2023
12M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	98.4 %	147.6 mg	02/02/2023	1129888	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA
18M	NA	NA	NA	102.2%	153.3mg	02/08/2023	1196450	12/09/2023
21M	NA	NA	NA	102.6 %	154.0 mg	01/11/2023	1230278	18/11/2023
24M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	102.5%	153.8mg	02/02/2024	1263298	05/03/2024
36M								
ASL								

Note: NA-Not Applicable. M-month. 15M NDMA Analysis performed from FG stock which was stored in 15°C to 25°C.

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

Remarks:

1. Initial to 12M results updated from 7710089A protocol no: TAB/MST/21/455/R2. 15M NDMA result updated from FG stock analysis. From 18M onwards stability incubation and analysis has been resumed as per protocol TAB/PYF/005/23/00.
2. 21M analysis shall be performed for data generation as per customer request.
3. Reference Deviation no: PYF/DR/2024/035 for 24M

Review Checkpoints:

1	If any OOS/OOT is recorded, investigation and disposition action is completed (OOS/OOT reference No.: NA)	☒ Yes ☒ No ☑ NA
2	If confirmed OOS/OOT, the following action (s) is recommended	
	• Change in specification limit	☒ Yes ☒ No ☑ NA
	• Shelf-life reduction	☒ Yes ☒ No ☑ NA
	• Any Other Action-(Specify if yes, add attachment if necessary)	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC or CAPA No.: - NA	
3	If any deviation is recorded, Deviation reference No.: PYF/DR/2024/035 for 24M Remarks (if any): Nil	
4	Shelf-life extension is recommended	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC No.: - NA)	

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 150 mg	**Batch size:** -	421052 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710089A	**SFG Code:** -	2007863		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	Dec-2021	**Exp. Date:**-	Nov-2024
Date of incubation: -	01/02/2022	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007863/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/005/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,36 and ASL months				

Conclusion: - The product **complies / ~~does not comply~~** with the specification till the time stability study is conducted/ shelf life of the product.

Comment (if any): Nil

[redacted]

Formulation Unit II - s47

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	CF-162mm-25OPA/50Alu/60PVC (1046201), Plain Alu. Foil-160/0.025mm-TOTAL 75GSM (1046203)			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Period / Test	Appearance	Identification A [by HPLC] [IH] / Identification A	Dissolution	Related Substances by LC-HRMS i) N-Nitroso dimethylamine (NDMA Impurity)	Sample pulled on	Reference A.R No.	Date of Release
Limit	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	Not more than 0.3 ppm	NA	NA	NA
Initial	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	91%, 92%, 97%, 96%, 97%, 98% AVG: 95%	s47 [redacted] ppm)	NA	40000289284	03/02/2022
03M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 88%, 99%, 88%,88%, 89%, 88%, Avg.:90%	s47 [redacted]	03/05/2022	1042422	15/09/2022
06M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 96%, 95%, 92%,96%, 95%, 96%, Avg.:95%	s47 ppm	03/08/2022	1073479	03/12/2022
09M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 82%, 93%, 86%, 84%, 93%, 93%, S2: 84%, 82%, 93%, 87%, 87%, 95%, Avg.: 88%	s47 ppm	03/11/2022	1102720	01/02/2023

Formulation Unit II - s47 [redacted]

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

12M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 90%, 99%, 92%, 94%, 97%, 83%, S2: 94%, 95%, 95%, 98%, 92%, 99%, Avg.: 94%	s47 [redacted] ppm	03/02/2023	1130424	05/05/2023
15M	NA	NA	NA	s47 [redacted] ppm	NA	NA	NA
18M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 98%, 97%, 97%, 95%, 97%, 86%, Avg.: 95%	s47 [redacted] ppm	03/08/2023	1196443	12/09/2023
21M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 98%, 95%, 98%, 90%, 92%, 91%, Avg.: 94%	s47 [redacted] ppm	03/11/2023	1230300	18/11/2023
24M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 93%, 92%, 99%, 100%, 89%, %, Avg.: 94%	s47 [redacted] **ppm@**	03/02/2024	1263300	NA
ASL							
36M							

Formulation Unit II - s47 [redacted]

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Period ↓ / Test	Related substances by UPLC						Sample pulled on	Reference A.R No.	Date of Release
	i) Impurity 1 (Impurity H)	ii) Impurity 2 (Impurity C)	iii) Impurity 3 (Impurity E)	iv) Impurity 4 (Impurity D)	v) Largest single unknown impurity	vi) Total impurities			
Limit	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.2%	Not more than 2.0%	NA	NA	NA
Initial	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BQL [LOQ = 0.032%]	0.0338%	0.0658%	NA	40000289284	03/02/2022
03M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.024%	0.02%	03/05/2022	1042422	15/09/2022
06M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.041%	0.066%	03/08/2022	1073479	03/12/2022
09M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ = 0.020%]	BQL	03/11/2022	1102720	01/02/2023

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

12M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.043 %	0.10 %	03/02/2023	1130424	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA	NA
18M	BDL [LOD = 0.007 %]	BQL [LOQ = 0.020 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.1 %	0.1 %	03/08/2023	1196443	12/09/2023
21M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.03 %	0.03 %	03/11/2023	1230300	18/11/2023
24M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	BQL [LOQ = 0.020%]	BQL	03/02/2024	1263300	NA
ASL									
36M									

STABILITY STUDY COMPILATION DATA

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Period / Test	Microbial limits			Assay by HPLC		Sample pulled on	Reference A.R No.	Date of Release
	i) Total aerobic microbial count	ii) Total combined yeast & molds count	iii) Escherichia coli	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine				
Limit	Not more than 1000 cfu/g	Not more than 100 cfu/g	Absent/g	300 mg - Not less than 95.0 % and not more than 105.0 %	300 mg - Not less than 285.0 mg and not more than 315.0 mg	NA	NA	NA
Initial	LT 10 cfu/g	LT 10 cfu/g	Absent/g	102.2%	306.7mg	NA	40000289284	03/02/2022
03M	NA	NA	NA	101.1%	303.3mg	03/05/2022	1042422	15/09/2022
06M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	100.6%	301.9mg	03/08/2022	1073479	03/12/2022
09M	NA	NA	NA	100.8%	302.3mg	03/11/2022	1102720	01/02/2023
12M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	98.9%	296.7mg	03/02/2023	1130424	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA
18M	NA	NA	NA	101.9 %	305.8 mg	03/08/2023	1196443	12/09/2023
21M	NA	NA	NA	102.8 %	308.4 mg	03/11/2023	1230300	18/11/2023
24M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	102.0%	306.0 mg	03/02/2024	1263300	NA
ASL								
36M								

NA-Not Applicable. M-month. 15M NDMA Analysis performed from FG stock which was stored in 15°C to 25°C.

Remarks:

Note 1:Initial to 12M results updated from 7710129A protocol no: TAB/MST/21/405/R2. 15M NDMA result updated from FG stock analysis. From 18M onwards stability incubation and analysis has been resumed as per protocol TAB/PYF/005/23/00.

s47 [redacted]

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Review Checkpoints:

1	If any OOS/OOT is recorded, investigation and disposition action is completed (OOS/OOT reference No.: PYF/OOS/2024/0008)	☑ Yes ☒ No ☒ NA
2	If confirmed OOS/OOT, the following action (s) is recommended	
	• Change in specification limit	☒ Yes ☒ No ☑ NA
	• Shelf-life reduction	☒ Yes ☒ No ☑ NA
	• Any Other Action-(Specify if yes, add attachment if necessary)	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC or CAPA No.: - NA	
3	If any deviation is recorded, Deviation reference No.: PYF/DR/2024/035 for 24M Remarks (if any): Nil	
4	Shelf-life extension is recommended	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC No.: - NA)	

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710129A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,21,24,ASL and 36 months				

Conclusion: - The product ~~**complies**~~ **/ does not comply@** with the specification till the time stability study is conducted/ shelf life of the product.

Comment (if any): @ FG and Reserve samples are tested which was stored in 15°C to 25°C and test results are 0.25 ppm and 0.23 ppm respectively.

STABILITY STUDY COMPILATION DATA

LONGTERM STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

Period / Test	Appearance	Identification A [by HPLC] [IH] / Identification A	Dissolution	Related Substances by LC-HRMS: i) N-Nitroso dimethylamine (NDMA Impurity)	Sample pulled on	Reference A.R No.	Date of Release
Limit	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	Not more than 0.3 ppm	NA	NA	NA
Initial	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1:100%, 100%, 100%,92%, 92%, 92% AVG:96%	s47 [redacted]	NA	40000289303	03/02/2022
03M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 96%, 92%, 98%, 99%, 87%, 87%, Avg.:93%	s47 [redacted]	03/05/2022	1042425	15/09/2022

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

06M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 94%, 99%, 93%, 93%, 94%, 96%, Avg.:95%	s47 [redacted] ppm	03/08/2022	1073482	03/12/2022
09M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 85%, 86%, 87%,92%, 96%, 97%, Avg.:90%	s47 [redacted] ppm	03/11/2022	1102724	10/03/2023
12M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 87%, 80%, 87%,87%, 79%, 82%, S2: 89%, 99%, 91%,90%, 91%, 101%, Avg.: 89%	s47 [redacted] ppm	03/02/2023	1130426	05/05/2023
15M	NA	NA	NA	s47 [redacted] ppm	NA	NA	NA
18M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1:89%,90%,90%,96%,89%,95% Avg: 91%	s47 [redacted] ppm	03/08/2023	1196444	12/09/2023
21M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 91%, 89%, 90%, 94%, 92%, 91% Avg.: 91%	s47 [redacted] ppm	03/11/2023	1230299	18/11/2023

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

24M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 93%, 95%, 95%, 95%, 99%, 99% , Avg.: 96%	0.27 ppm	03/02/2024	1263301	05/03/2024
ASL							
36M							

STABILITY STUDY COMPILATION DATA

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 / 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

Period / **Test**	**Related substances by UPLC**						**Sample pulled on**	**Reference A.R No.**	**Date of Release**
	i) Impurity 1 (Impurity H)	**ii) Impurity 2 (Impurity C)**	**iii) Impurity 3 (Impurity E)**	**iv) Impurity 4 (Impurity D)**	**v) Largest single unknown impurity**	**vi) Total impurities**			
Limit	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.2%	Not more than 2.0%	NA	NA	NA
Initial	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD=0.011%]	0.036%	0.070%	NA	40000289303	03/02/2022
03M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.022%	0.02%	03/05/2022	1042425	15/09/2022
06M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.045%	0.073%	03/08/2022	1073482	03/12/2022
09M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.020%	0.02%	03/11/2022	1102724	10/03/2023
12M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.011%]	0.043 %	0.10 %	03/02/2023	1130426	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA	NA

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

18M	BDL [LOD = 0.007 %]	BQL [LOQ = 0.020 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.1 %	0.1 %	03/08/2023	1196444	12/09/2023
21M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.03 %	0.05 %	03/11/2023	1230299	18/11/2023
24M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	BQL (LOQ=0.020%)	BQL	03/02/2024	1263301	05/03/2024
ASL									
36M									

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

Period / Test	Microbial limits			Assay by HPLC		Sample pulled on	Reference A.R No.	Date of Release
	i) Total aerobic microbial count	ii) Total combined yeast & molds count	iii) Escherichia coli	Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine				
Limit	Not more than 1000 cfu/g	Not more than 100 cfu/g	Absent/g	300 mg - Not less than 95.0 % and not more than 105.0 %	300 mg - Not less than 285.0 mg and not more than 315.0 mg	NA	NA	NA
Initial	LT 10 cfu/g	LT 10 cfu/g	Absent/g	102.4 %	307.1 mg	NA	40000289303	03/02/2022
03M	NA	NA	NA	103.3 %	309.8 mg	03/05/2022	1042425	15/09/2022
06M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	100.3 %	300.9 mg	03/08/2022	1073482	03/12/2022
09M	NA	NA	NA	100.7 %	302.2 mg	03/11/2022	1102724	10/03/2023
12M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	100.0 %	300.0 mg	03/02/2023	1130426	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA
18M	NA	NA	NA	101.5 %	304.4 mg	03/08/2023	1196444	12/09/2023
21M	NA	NA	NA	102.2 %	306.6 mg	03/11/2023	1230299	18/11/2023
24M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	102.8 %	308.5 mg	03/02/2024	1263301	05/03/2024
ASL								
36M								

Note: NA-Not Applicable. M-month.15M NDMA Analysis performed from FG stock which was stored in 15°C to 25°C.

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted] **LONGTERM STABILITY STUDY COMPILATION DATA**

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

Remarks:

Note 1:Initial to 12M results updated from 7710130A protocol no: TAB/MST/21/421/R2. 15M NDMA result updated from FG stock analysis. From 18M onwards stability incubation and analysis has been resumed as per protocol TAB/PYF/011/23/00.

Note 2: Deviation reference No.: PYF/DR/2024/035 for 24M

Review Checkpoints:

1	If any OOS/OOT is recorded, investigation and disposition action is completed (OOS/OOT reference No.: NA)	☒ Yes ☒ No ☑ NA
2	If confirmed OOS/OOT, the following action (s) is recommended	
	• Change in specification limit	☒ Yes ☒ No ☑ NA
	• Shelf-life reduction	☒ Yes ☒ No ☑ NA
	• Any Other Action-(Specify if yes, add attachment if necessary)	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC or CAPA No.: - NA	
3	If any deviation is recorded, Deviation reference No.: PYF/DR/2024/035 for 24M Remarks (if any): Nil	
4	Shelf-life extension is recommended	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC No.: - NA)	

STABILITY STUDY COMPILATION DATA

Formulation Unit II - s47 [redacted]

LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710130A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24, ASL and 36 months				

Conclusion: - The product **complies** / ~~**does not comply**~~ with the specification till the time stability study is conducted/ shelf life of the product.

Comment (if any): Nil

s47

Formulation Unit II - s47

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 / 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

Period / **Test**	**Appearance**	**Identification A [by HPLC] [IH] / Identification A**	**Dissolution**	**Related Substances by LC-HRMS** i) N-Nitroso dimethylamine (NDMA Impurity)	**Sample pulled on**	**Reference A.R No.**	**Date of Release**
Limit	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	By HPLC: The retention time of the major peak in the chromatogram of the sample preparation corresponds to that of the major peak in the chromatogram of the standard preparation as obtained in the assay.	By UV: Not less than 85 % (Q=80) of the labeled amount of drug is dissolved in 45 minutes	Not more than 0.3 ppm	NA	NA	NA
Initial	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1:98%, 94%,95%, 96%, 92%,99% Avg: 96%	s47	NA	40000289362	03/02/2022
03M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 91%, 96%, 87%,92%, 92%, 91%, Avg.:91%	s47	03/05/2022	1042428	15/09/2022
06M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 90%, 91%, 91%,91%, 90%, 93%, Avg.:91%	s47 ppm	03/08/2022	1073485	12/10/2022

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

09M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 97%, 94%, 95%,90%, 95%, 86%, Avg.:93%	s47 [redacted] ppm	03/11/2022	1102728	10/03/2023
12M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 94%, 95%, 93%,91%, 94%, 95%, Avg.:94%	s47 [redacted] ppm	03/02/2023	1130428	05/05/2023
15M	NA	NA	NA	s47 [redacted] ppm	NA	NA	NA
18M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side.	Complies	S1: 96%, 95%, 95%, 83%, 89%, 94%, S2: 93%, 100%, 95%, 100%, 97%, 93%, Avg.: 94%	s47 [redacted] ppm	03/08/2023	1196446	12/09/2023
21M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side	Complies	S1: 94%, 95%, 93%, 89%, 92%, 94% , Avg.: 93%	s47 [redacted] ppm	03/11/2023	1230301	18/11/2023

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

24M	White film coated oblong tablet, embossed with '300' on one side and plain on the other side	Complies	S1: 99%, 99%, 99%, 95%, 95%, 97% , Avg.: 97%	0.20 ppm	03/02/2024	1263302	05/03/2024
ASL							
36M							

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

Period / **Test**	**Related substances by UPLC**						**Sample pulled on**	**Reference A.R No.**	**Date of Release**
	i) Impurity 1 (Impurity H)	**ii) Impurity 2 (Impurity C)**	**iii) Impurity 3 (Impurity E)**	**iv) Impurity 4 (Impurity D)**	**v) Largest single unknown impurity**	**vi) Total impurities**			
Limit	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.3%	Not more than 0.2%	Not more than 2.0%	NA	NA	NA
Initial	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BQL (LOQ=0.032%)	0.037%	0.07%	NA	40000289362	03/02/2022
03M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.024%	0.02%	03/05/2022	1042428	15/09/2022
06M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	0.043%	0.068%	03/08/2022	1073485	12/10/2022
09M	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.007%]	BDL [LOD = 0.011%]	BQL [LOQ=0.020%]	BQL	03/11/2022	1102728	10/03/2023

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

12M	BDL [LOD = 0.007%]	BQL [LOQ = 0.020%]	BQL [LOQ = 0.020%]	BDL [LOD = 0.011%]	0.044 %	0.10 %	03/02/2023	1130428	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA	NA
18M	BDL [LOD = 0.007 %]	BQL [LOQ = 0.020 %]	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.1 %	0.1 %	03/08/2023	1196446	12/09/2023
21M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	0.03 %	0.03 %	03/11/2023	1230301	18/11/2023
24M	BDL [LOD = 0.007 %]	BQL (LOQ=0.020%)	BDL [LOD = 0.007 %]	BDL [LOD = 0.011 %]	BQL (LOQ=0.020%)	BQL	03/02/2024	1263302	05/03/2024
ASL									
36M									

s47 [redacted]

Formulation Unit II - s47 [redacted]

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

Period ↓ **Test** →	**Microbial limits**			**Assay by HPLC**		**Sample pulled on**	**Reference A.R No.**	**Date of Release**
	i) Total aerobic microbial count	**ii) Total combined yeast & molds count**	**iii) Escherichia coli**	**Each film coated tablet contains Ranitidine Hydrochloride equivalent to Ranitidine**				
Limit	Not more than 1000 cfu/g	Not more than 100 cfu/g	Absent/g	300 mg - Not less than 95.0 % and not more than 105.0 %	300 mg - Not less than 285.0 mg and not more than 315.0 mg	NA	NA	NA
Initial	LT 10 cfu/g	LT 10 cfu/g	Absent/g	102.4 %	307.2 mg	NA	40000289362	03/02/2022
03M	NA	NA	NA	100.6 %	301.9 mg	03/05/2022	1042428	15/09/2022
06M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	99.6 %	298.9 mg	03/08/2022	1073485	12/10/2022
09M	NA	NA	NA	100.7 %	302.1 mg	03/11/2022	1102728	10/03/2023
12M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	99.8 %	299.4 mg	03/02/2023	1130428	05/05/2023
15M	NA	NA	NA	NA	NA	NA	NA	NA
18M	NA	NA	NA	101.5 %	304.5 mg	03/08/2023	1196446	12/09/2023
21M	NA	NA	NA	102.6 %	307.7 mg	03/11/2023	1230301	18/11/2023
24M	LT 10 cfu/g	LT 10 cfu/g	Absent/g	101.0%	302.9 mg	03/02/2024	1263302	05/03/2024
ASL								
36M								

Note: NA-Not Applicable. M-month. 15M NDMA analysis performed from FG stock.

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47			**API source/Batch No.**	s47 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

Remarks:
Note 1: Initial to 12M results updated from 7710131A (Protocol no: TAB/MST/21/422/R2). 15M NDMA result updated from FG stock analysis. 18M analysis performed as per protocol TAB/PYF/011/23/00.
Note2: Refer OOT No: PYF/OOT/2023/0199 for dissolution test 18M Interval.
Note 3: Refer Deviation No: PYF/DR/2023/0203 for 18M Interval and PYF/DR/2024/035 for 24M

Review Checkpoints:

1	If any OOS/OOT is recorded, investigation and disposition action is completed. (OOS/OOT reference No.: PYF/OOT/2023/0199)	☑ Yes ☒ No ☒ NA
2	If confirmed OOS/OOT, the following action (s) is recommended	
	• Change in specification limit	☒ Yes ☒ No ☑ NA
	• Shelf-life reduction	☒ Yes ☒ No ☑ NA
	• Any Other Action-(Specify if yes, add attachment if necessary)	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC or CAPA No.: - NA	
3	If any deviation is recorded, Deviation reference No.: PYF/DR/2023/0203 for 18M and PYF/DR/2024/035 for 24M Remarks (if any): Nil	
4	Shelf-life extension is recommended	☒ Yes ☒ No ☑ NA
	(If yes, Reference CC No.: - NA)	

s47 [redacted]

Formulation Unit II - s47 [redacted]

STABILITY STUDY COMPILATION DATA
LONGTERM STABILITY STUDY COMPILATION DATA

Product: -	Ranitidine Tablets 300 mg	**Batch size:** -	210526 Tablets	**Stability conditions:** -	25°C ± 2°C / 60%RH ± 5%RH
Batch No: -	7710131A	**SFG Code:** -	2007869		
Mfg. Location: -	Formulation Unit II - s47 [redacted]	**Mfg. Date:** -	JAN-2022	**Exp. Date:** -	DEC-2024
Date of incubation: -	03/02/2023	**Mfg. for:** -	s47 [redacted]	**Market:** -	RSA
Specification No: -	2007869/SLS/R1	**Effective date:** -	13/07/2023	**Protocol No.:** -	TAB/PYF/011/23/00
Version No: -	R3	**Pack details:** -	Blister pack 14s	**Orientation:** -	Horizontal
Primary Packaging material: -	s47 [redacted]			**API source/Batch No.**	s47 [redacted] 10000424418(CRDE210007) 10000424419 (CRDE210008)
Frequency of Testing: -	0, 3, 6, 9, 12, 15,18,24,ASLand 36 months				

Conclusion: - The product **complies / ~~does not comply~~** with the specification till the time stability study is conducted/ shelf life of the product.

Comment (if any): Nil

Request for Information: 30 January 2024
Reply Due Date: 8 March 2024
Actual Reply Date: 6 March 2024

Submission ID: PM-2023-05323-1-1 PCE2
File No: 2012/021274

Response

TGA Question 1.

1. Regarding the proposed drug product specifications:

   a. It is noted in the summary of changes provided in the cover letter that both current identification tests by NIR and HPLC will be retained, in addition to the proposed TLC and chloride test methods. However, the NIR test method was not included in the proposed drug product specifications provided for both strengths. Please clarify this and if necessary, revise the specifications as appropriate.

      Aspen Response
      The NIR test for ID has been removed from the finished product specification.

   b. The proposed limits for total impurities (NMT 2.0%) and specified Impurities C, D, E and H (each at NMT 0.3%) determined by the proposed UPLC method are higher than the current BP monograph limits for total impurities (NMT 1.0%) and any single secondary impurities (NMT 0.2%). Please tighten the proposed limits for total and individual specified impurities (C, D, E and H) in line with current BP monograph and provide revised specifications and supporting documents as appropriate.

      Aspen Response
      The finished product specification has been updated in line with total and individual specified impurities (C, D, E and H) of the current BP monograph and a revised specification included in 32p51.

   c. Please provide appropriate cross-validation data that demonstrates the proposed in-house UPLC method for related substances is superior or at least equivalent to the test method described in the current BP monograph for ranitidine tablets.

      A cross-validation data may be acquired in accordance with ICH Q1 between the proposed UPLC and the current BP monograph methods (or current in-house HPLC method) or by comparative batch analyses between the two methods on at least three **aged batches** of the drug product.

      Aspen Response
      A method equivalency report has been generated that demonstrates the proposed in-house UPLC method for related substances is equivalent to the test method described in the current BP monograph for ranitidine tablets.
      The report is included in 32p53.

TGA Question 2.

Given the drug product manufacturing process at the proposed [redacted] site was validated only for the proposed [redacted] Kg batch size, and NOT for the current [redacted] Kg maximum batch size, manufacture of commercial batches of the drug product intended for supply in Australia can only be carried out on the validated [redacted] Kg batch size. Please update the proposed batch formula document by deleting the current [redacted] Kg batch size.

Aspen Response

Aspen Australia agrees that only the validated [redacted] Kg batch size will be commercialised until a regulatory action is taken (and TGA approved) to add a lager batch size.
Please refer to 32p3 for the revised 'batch-formula'.

TGA Question 3.

It is noted that only expired ranitidine drug products were used as reference materials in the comparative dissolution profile data provided. Please provide for review recent certificate of analyses for the expired ranitidine reference materials to ensure the materials are still of acceptable quality.

Aspen Response

The expired ranitidine drug product samples have not been retested, because they are expired and not expected to meet the quality standard of the finished product expiry specification. A justification for using the expired product in comparative dissolution testing was provided in 32p33 process-validation of sequence 0014.

TGA Question 4.

Regarding the proposed drug product shelf-life:

a. Both 18 and 24 months shelf-lives are proposed in the cover letter. Please clarify which of these two is correct and provide the relevant Module 3.2.P.8.1 Stability summary and Module 3.2.P.8.2 Post-Approval Stability Protocol/Commitment documents to reflect the proposed shelf-life.
Given the history of the product and the fact that only 18 months of long-term stability data was provided, it is recommended that the proposed shelf-life reflects the current available 18 months stability data.

Aspen Response

21 and 24 month stability data is now available and presented below:

Ranitidine tablets Stability - NDMA results (ppm)											
S No	Product Name	Batch No	Initial	03M	06M	09M	12M	18M	21M	24M	NMDA ↑ over shelf life
1	Ranitidine tablets 150mg	7710087A	BDL *<0.011 ppm*	BQL *<0.033 ppm*	0.06	0.04	0.16	0.09	0.15	0.24	0.24-0.011= 0.23
2		7710088A	BDL *<0.011 ppm*	BQL *<0.033 ppm*	0.05	0.04	0.13	0.08	0.13	0.19	0.19-0.011= 0.18
3		7710089A	BDL *<0.011 ppm*	BQL *<0.033 ppm*	0.05	0.05	0.16	0.11	0.14	0.24	0.24 -0.011= 0.23
4	Ranitidine tablets 300mg	7710129A	BDL *<0.011 ppm*	BQL *<0.033 ppm*	0.14	0.08	0.23	0.13	0.22	0.24*	0.24-0.011= 0.23
5		7710130A	BDL *<0.011 ppm*	BQL *<0.033 ppm*	0.06	0.05	0.16	0.10	0.15	0.24	0.24 -0.011= 0.23
6		7710131A	BDL *<0.011 ppm*	BQL *<0.033 ppm*	0.06	0.04	0.14	0.08	0.15	0.23	0.23-0.011= 0.22

**Reserve sample and FG sample testing in lieu of stability sample (average result)*

Shelf life NDMA Specification Limit – NMT 0.32 ppm

Proposed API limits – NMT s47 ppm

From the stability data – we can see that the maximum increase in NDMA across 21/24 month SL was s47 ppm

Therefore the maximum release limits of the FP, to allow the s47 ppm increase over SL is s47 [redacted], however – Aspen proposes to tighten further

Proposed FP* release limit is s47 ppm then the allowable increase from release to expiry is s47 ppm s47 [redacted] *24 months shelf life when stored below 25°C

Therefore, based on the stability data and the new NDMA release limits in the API, Aspen proposes the following release and expiry limits or NDMA in the finished product:

Strength	Proposed Release Limits	Proposed Expiry Limits
150mg	NMT s47 [redacted] NDMA	NMT 0.32ppm NDMA
300mg	NMT s47 [redacted] NDMA	NMT 0.32ppm NDMA

Revised specification included in 32p51.

Updated stability data and report included in 32p8.

b. Please provide for review 0 to 6 months of stability data for each strength of the drug product stored under accelerated storage conditions in accordance with ICH guidelines.

Aspen Response

The product is already well characterised and established with regard to its general stability and real time data has been presented in the submission showing its full compliance with specifications.
It is also well known that the presence of nitrosamines increases quickly in the presence of heat.
So, the generation of accelerated data was not initiated because 'real time' data was presented.

However, Aspen gives an assurance that the first 3 commercial batches manufactured post approval will be placed on stability, including an accelerated study and an assurance is given that (other than for NDMA) any OOS will be reported to the TGA.

TGA Question 5.

The black square with red graphic on the main label depicting the target organ (stomach) for the drug product is considered **unacceptable** as it has potential implications for promotional aspects with regards to suggested efficacy. This is in accordance with TGA interpretation of Therapeutic Goods (Therapeutic Goods Advertising Code) Instrument 2021.

Please revise the proposed labels (for products AUST 53323 and 53324) by deleting the graphic. Please also provide annotated copies of the current labels.

Aspen Response

The graphic has been removed from the proposed carton labels and and they have been included in the relevant section of m1.3.

s 22 in the OTC branch has also been in contact with Aspen regarding the OTC SKU's of this product.

TGA Question 6.

Please update Section 6.4 of the PI to include the precautionary statement "Protect from heat" (or "light", as appropriate).

Updated 31 January 2024 - With regards to the PI, you have also included other ZANTAC ranitidine products in dosage forms including effervescent tablets, syrup and injection. However, these additional ZANTAC products are still suspended indefinitely from the ARTG and are not included in this application. As such, please update the PI by deleting these additional products (and any specific reference, as appropriate). These products can be added to the PI at a later stage when they are reinstated to the ARTG.

To ensure the quality aspect of the PI is maintained, please note that the revised PI will be referred for clinical evaluation and further questions may arise.

Aspen Response

The PI has been updated in line with the evaluator's comments. An annotated and clean version are included in m1.3

TGA Question 7. (received via email on 31 January 2024)
As we discussed earlier on the phone, please tighten the release limit for NDMA impurity in the specifications of both strengths of the drug product.

From the 18 months long-term stability data provided, the maximum observed increase in NDMA level was at the 12 months timepoint at s47 ppm for the 150 mg strength and s47 ppm for the 300 mg strength products. Please ensure that any proposed release limit for NDMA (for instance, s47 ppm) allows for the maximum observed increase over the proposed shelf-life – i.e. if the release limit is s47 ppm, then the allowable increase from release to expiry is s47 .

Aspen Response
Please cross reference Aspen's response to Question 4
Shelf life NDMA Specification Limit – NMT 0.32 ppm
Proposed API limits – NMT s47 ppm
From the stability data – we can see that the maximum increase in NDMA across 21/24 month SL was s47 ppm
Therefore the maximum release limits of the FP, to allow the s47 ppm increase over SL is s47 ppm, however – Aspen proposes to tighten further
Proposed:
***FP* release limit is s47 ppm then the allowable increase from release to expiry is s47 ppm s47**
24 months shelf life when stored below 25°C.

End of Response