Attachment 1: Product information for AusPAR Selincro Lundbeck Australia Pty Ltd PM-2013-02690-1-1 Final 9 August 2016. This Product Information was approved at the time this AusPAR was published.

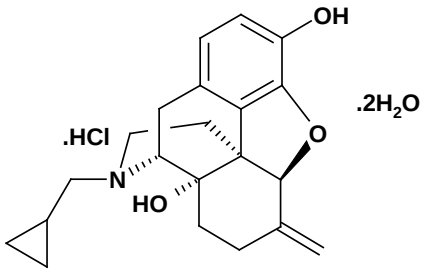
PRODUCT INFORMATION

SELINCRO®

NAME OF THE MEDICINE

Nalmefene

Nalmefene is present in nalmefene film-coated tablets as nalmefene hydrochloride dihydrate. The chemical name of nalmefene hydrochloride dihydrate is 17-(cyclopropylmethyl)-4,5α-epoxy-6-methylene-morphinan-3,14-diol hydrochloride dihydrate and has the following structural formula:



Molecular formula: $C_{21}H_{25}NO_3$ HCl.$2H_2O$
Molecular mass: 411.92
CAS number: 1228646-70-5

Molecular mass (anhydrous nalmefene free base): 339.43
CAS number (anhydrous nalmefene free base): 55096-26-9

DESCRIPTION

Nalmefene hydrochloride dihydrate is a white to almost white crystalline powder. It is an alkaloid derivative from a natural source; the configuration of the chiral centres is therefore fixed and defined by the natural structure. Only one crystal form of nalmefene hydrochloride dihydrate has been identified.

Nalmefene hydrochloride dihydrate is not hygroscopic and water is not absorbed, even at 95% relative humidity. Nalmefene hydrochloride dihydrate is very soluble in water: 132 mg/mL corresponding to 109 mg of nalmefene base/mL, giving pH = 5.9 in the saturated solution.

Nalmefene is an ampholyte with pKa= 9.9 (± 0.3) for the acid, and pKa= 9.2 (± 0.1) for the base.

At pH values less than 7.4, nalmefene has a log D (n-octanol/water) between 0.05 and 1.3.

SELINCRO is available as film-coated tablets each containing nalmefene hydrochloride dihydrate 21.9 mg equivalent to nalmefene 18 mg.

Excipients

Nalmefene film-coated tablets contain microcrystalline cellulose, lactose anhydrous, crospovidone, magnesium stearate and Opadry complete film coating system Opadry OY-S-28849 White.

PHARMACOLOGY

Pharmacodynamics

Nalmefene is an opioid system modulator with a distinct μ, δ, and κ receptor profile.

- *In vitro* studies have demonstrated that nalmefene is a selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor.
- *In vivo* studies have demonstrated that nalmefene reduces alcohol consumption, possibly by modulating cortico-mesolimbic functions.

A positron emission tomography (PET) study in healthy subjects was used to assess the brain occupancy of nalmefene at the opioid receptors. In this study, a very high occupancy at the μ opioid receptors (94% to 100%) was observed 3 hours after single and repeated daily dosing with 18 mg nalmefene. The high occupancy (83% to 100%) persisted 26 hours after dosing.

The administration of nalmefene is not associated with development of tolerance or dependence. In subjects physically dependent on opioids, nalmefene will precipitate withdrawal symptomatology. Nalmefene is a competitive antagonist at μ and δ opioid receptors and when co-administered with opioids is anticipated to reduce the action of opioids given for analgesia.

Pharmacokinetics

<u>Absorption</u>

Nalmefene is rapidly absorbed after a single oral administration of 18 mg, with a peak concentration (C_{max}) of 16.5 ng/ml after approximately 1.5 hours and an exposure (AUC) of 131 ng·h/mL. The absolute oral bioavailability of nalmefene has not been fully assessed but has been estimated to be ~40%. Administration of high-fat food increases the total exposure

(AUC) by 30% and the peak concentration (C_{max}) by 50%; the time to peak concentration (t_{max}) is delayed by 30 min (t_{max} is 1.5 hours). This change is considered unlikely to be of clinical relevance.

Distribution

The average protein-bound fraction of nalmefene in plasma is approximately 30%. The estimated volume of distribution (Vd/F) is approximately 3200 L. Nalmefene crosses the blood-brain barrier.

Metabolism

Following oral administration, nalmefene undergoes extensive, rapid metabolism to the major metabolite nalmefene 3-O-glucuronide. UGT2B7 is the primary liver enzyme responsible for the conversion of nalmefene to nalmefene 3-O-glucuronide *in vitro*. Furthermore, UGT1A3 and UGT1A8 may also contribute to this pathway. A small proportion of nalmefene is converted to nalmefene 3-O-sulphate by sulphation and to nornalmefene by CYP3A4/5. Nornalmefene is further converted to nornalmefene 3-O-glucuronide and nornalmefene 3-O-sulphate. The metabolites are considered unlikely to contribute significantly to the pharmacological effect of nalmefene on the opioid receptors in humans. Although nalmefene 3-O-sulphate has similar affinity for opioid receptors as nalmefene, it is present in human plasma at concentrations less than 10% of that of nalmefene and is thus considered unlikely to be a major contributor to the pharmacological effect of nalmefene. Other metabolites, including nornalmefene 3-O-glucuronide and nornalmefene 3-O-sulfate, as well as nalmefene 3-O-glucuronide, have much lower affinities for the opioid receptors than nalmefene.

Excretion

Metabolism by glucuronide conjugation is the primary mechanism of clearance for nalmefene, with renal excretion being the main route of elimination of nalmefene and its metabolites. 54% of the total dose is excreted in the urine as nalmefene 3-O-glucuronide, while nalmefene and its other metabolites are present in the urine in amounts of less than 3% each. The oral clearance of nalmefene (CL/F) was estimated as 169 L/h and the terminal half-life was estimated as 12.5 hours.

From distribution, metabolism, and excretion data, it appears that nalmefene has a high hepatic extraction ratio.

Linearity/non-linearity

Nalmefene exhibits a dose-independent linear pharmacokinetic profile in the dose interval of 18.06 mg to 72.24 mg, with a 4.4 times increase in C_{max} and a 4.3 times increase in $AUC_{0\text{-}tau}$ (at or near steady state).

Nalmefene does not exhibit substantial pharmacokinetic differences between sexes, between young and elderly, or between ethnic groups. However, body size seems to affect the clearance of nalmefene to a minor degree (clearance increases with increasing body size), but this is considered unlikely to be of clinical relevance.
The variability of the pharmacokinetic parameters was up to ~ 45% for the inter-subject variability, and up to ~ 31% for the intra-subject variability.

Special populations

Renal impairment

No data after oral administration in patients with renal impairment are available. Administration of 1 mg nalmefene IV in patients with severe renal impairment resulted in a 1.6-fold larger exposure (dose-adjusted AUC_{inf}), and a lower dose-adjusted C_{max} (by a factor of approximately 2.1 to 4.6) than those in healthy control subjects given 2 mg nalmefene IV in a different study. The elimination half-life (26 hours) was longer than that in healthy subjects (10 hours) (see CONTRAINDICATIONS and PRECAUTIONS).

Hepatic impairment

Administration of a single dose of nalmefene 18.06 mg to patients with mild or moderate hepatic impairment increased exposure relative to that in healthy subjects. In patients with mild hepatic impairment, exposure increased 1.5 times and oral clearance decreased by approximately 35%. In patients with moderate hepatic impairment, exposure increased 2.9 times for AUC and 1.7 times for C_{max}, while oral clearance decreased by approximately 60%. No clinically relevant changes were seen in t_{max} or elimination half-life for any of the groups.

Pharmacokinetic data after oral administration of nalmefene to patients with severe hepatic impairment are not available (see CONTRAINDICATIONS and PRECAUTIONS).

Elderly

No specific study with oral dosing has been conducted in patients ≥65 years of age. A study with IV administration in the elderly suggested that there were no relevant changes

in the pharmacokinetics as compared to results observed in other studies (see DOSAGE & ADMINISTRATION and PRECAUTIONS).

CLINICAL TRIALS

The efficacy of SELINCRO in reducing alcohol consumption in patients with alcohol dependence (DSM-IV) was evaluated in two efficacy studies, Study 1 (12014A) and Study 2 (12023A). Patients with a history of delirium tremens, hallucinations, seizures, significant psychiatric comorbidity, or significant abnormalities of liver function as well as those with significant physical withdrawal symptoms at screening or randomisation were excluded. The majority (80%) of the patients included had a high or very high Drinking Risk Level (DRL) (alcohol consumption >60 g/day for men and >40 g/day for women according to the WHO DRLs of alcohol consumption. 10 g alcohol = 1 standard drink) at screening, of these 65% maintained a high or very high DRL between screening and randomisation.

Both studies were randomised, double-blind, parallel-group and placebo-controlled, and after 6 months of treatment, patients who received SELINCRO were re-randomised to receive either placebo or SELINCRO in a 1-month run-out period. At the initial visit, the patients' clinical status, social situation, and alcohol consumption pattern were evaluated (based on patient reporting). At the randomisation visit, which occurred 1 to 2 weeks later, the DRL was re-assessed and treatment with SELINCRO was initiated together with a psychosocial intervention (BRENDA) focused on treatment adherence and reduction of alcohol consumption. SELINCRO was prescribed as-needed, which resulted in patients taking SELINCRO, on average, approximately half of the days.

The efficacy of SELINCRO was measured using two co-primary endpoints: the change from baseline to Month 6 in the monthly number of heavy drinking days (HDDs) and the change from baseline to Month 6 in the daily total alcohol consumption (TAC). An HDD was defined as a day with a consumption ≥60 g of pure alcohol for men and ≥40 g for women.

A significant reduction in the number of HDDs and TAC occurred in some patients in the period between the initial visit (screening) and randomisation due to non-pharmacological effects.

In Studies 1 (12014A; n=579) and 2 (12023A; n=655), 18%, and 33%, of the total population, respectively, considerably reduced their alcohol consumption in the period between screening and randomisation. Of the patients with a high or very high DRL at baseline, 35% experienced improvement due to non-pharmacological effects in the period between the initial visit (screening) and randomisation.

Therefore, the patients who maintained a high or very high DRL at randomisation were defined *post hoc* as the target population. In this *post hoc* population, the treatment effect was larger than that in the total population (patients with at least medium DRL at screening). The efficacy results for the total population are presented below followed by the results of the target population.

Efficacy results for the total population - Patients with at least medium DRL at Screening

In Study 1, the proportion of patients who withdrew was higher in the SELINCRO group than in the placebo group (48% versus 26%, respectively). In Study 2, the proportion of patients who withdrew was similar in the SELINCRO group and the placebo group (36% versus 30%, respectively).

Table 1 shows efficacy results at Month 6 based on the primary mixed model repeated measures (MMRM) analysis.

Table 1: Results for the Co-primary Efficacy Variables at Month 6 (FAS, MMRM) – Total Population

Variable Treatment Group	Baseline		Change from Baseline to Month 6		Difference to PBO		
	N	Mean ± SD	N	Mean ± SE	Mean	95% CI	p-value
Number of HDDs (days/month)							
Study 1							
PBO	289	19.6 ± 6.9	213	-8.9 ± 0.6			
NMF	290	19.4 ± 7.3	152	-11.2 ± 0.6	-2.3	[-3.8; -0.8]	0.002
Study 2							
PBO	326	18.3 ± 7.0	229	-10.6 ± 0.5			
NMF	329	19.8 ± 6.8	212	-12.3 ± 0.5	-1.7	[-3.1; -0.4]	0.012
TAC (g/day)							
Study 1							
PBO	289	85 ± 42	213	-39.7 ± 2.2			
NMF	290	84 ± 42	152	-50.7 ± 2.4	-11.0	[-16.8; -5.1]	<0.001
Study 2							
PBO	326	89 ± 48	229	-54.1 ± 2.2			
NMF	329	93 ± 46	212	-59.0 ± 2.3	-5.0	[-10.6; 0.7]	0.088

FAS = Full Analysis Set; Baseline values are based on the FAS

Efficacy results for the target population defined *post-hoc*. Patients who maintained a high or very high DRL at randomisation

In Study 1, the proportion of patients who withdrew was higher in the SELINCRO group than in the placebo group (50% versus 32%, respectively). In Study 2, the proportion of patients who withdrew was similar in the SELINCRO group and the placebo group (30% versus 28%, respectively).

Table 2 shows efficacy results at Month 6 based on the primary MMRM analysis. Patients treated with SELINCRO reduced their TAC by approximately 60% and the HDDs by approximately 55% relative to the baseline values.

In both studies, the effect of SELINCRO was observed at Month 1 and maintained throughout the treatment period.

Table 2: Results for the Co-primary Efficacy Variables at Month 6 (FAS, MMRM) – Target Population, that is, Patients with a High or Very High DRL at Baseline and Randomisation

Variable Treatment Group	Baseline		Change from Baseline to Month 6		Difference to PBO		
	N	Mean ± SD	N	Mean ± SE	Mean	95% CI	p-value
Number of HDDs (days/month)							
Study 1							
PBO	167	23.1 ± 5.4	114	-8.0 ± 1.0			
NMF	171	23.0 ± 5.9	85	-11.6 ± 1.0	-3.7	[-5.9; -1.5]	0.001
Study 2							
PBO	155	21.6 ± 6.4	111	-10.2 ± 0.9			
NMF	148	22.7 ± 6.0	103	-12.9 ± 0.9	-2.7	[-5.0 -0.3]	0.025
TAC (g/day)							
Study 1							
PBO	167	99 ± 40	114	-40.0 ±3.9			
NMF	171	102 ± 43	85	-58.3 ± 4.1	-18.3	[-26.9; -9.7]	<0.001
Study 2							
PBO	155	108 ± 47	111	-60.1 ± 4.0			
NMF	148	113 ± 48	103	-70.4 ± 4.0	-10.3	[-20.2; -0.5]	0.040

FAS = Full Analysis Set; Baseline values are based on FAS.

Responder analyses of the pooled data from the two studies are provided in Table 3.

Table 3: Pooled Responder Analysis Results in Patients with a High or Very High DRL at Screening and Randomisation

Response	Placebo	Nalmefene	Odds Ratio (95% CI)	p-value
MMRM[a]				
TAC R70[b]	25.8%	38.2%	1.88 (1.32; 2.70)	<0.001
0-4 HDD[c]	20.5%	30.4%	1.91 (1.30; 2.83)	0.001
NR[d]				
TAC R70[b]	19.9%	25.4%	1.44 (0.97; 2.13)	0.067
0-4 HDD[c]	16.8%	22.3%	1.54 (1.02; 2.35)	0.040

a Analysis uses patient-predicted TAC or HDD values derived from the MMRM model in the primary analysis for patients who withdrew
b ≥70% reduction from baseline in TAC at Month 6 (28-day period)
c 0 to 4 HDDs/month at Month 6 (28-day period)
d Analysis treats patients who withdrew as non-responder

There are limited efficacy data available beyond 6 months.

INDICATIONS

SELINCRO is indicated for the reduction of alcohol consumption in adult patients with alcohol use disorder who have an average daily consumption of alcohol of more than 60 g for men and more than 40 g for women.

SELINCRO should be prescribed only if the patient has failed to achieve an adequate response following psychosocial intervention for at least 2 weeks.

SELINCRO should be prescribed in conjunction with continuing psychosocial support focused on treatment adherence and reducing alcohol consumption. SELINCRO is not suitable for patients with physical withdrawal syndrome or who require immediate detoxification.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in DESCRIPTION -Excipients.

Patients taking opioid agonists (such as opioid analgesics, opioids for substitution therapy with opioid agonists (e.g. methadone) or partial agonists (e.g. buprenorphine)).

Patients with current opioid dependence or opioid abuse due to the risk of precipitating an acute opioid withdrawal syndrome.

Patients with acute opioid withdrawal syndrome.

Patients with severe hepatic impairment (Child-Pugh classification).

Patients with severe renal impairment (eGFR <30 ml/min per 1.73 m^2).

Patients with a recent history of acute alcohol withdrawal syndrome (including hallucinations, seizures, and delirium tremens).

PRECAUTIONS

SELINCRO has not been shown to be effective in patients who are not provided with psychosocial intervention. SELINCRO should be prescribed only to those patients who continue to consume more than 60 g alcohol daily (men) or 40 g daily (women). Treatment with SELINCRO should be reviewed on an ongoing basis (e.g. monthly). After no more than 24 weeks of treatment patients should be reassessed to determine if continuing treatment with SELINCRO is required. There is limited long term data available and caution is advised if SELINCRO is prescribed for more than 24 weeks. Patients who do not show an adequate response should be offered treatment alternatives as part of an overall treatment care plan.

SELINCRO is not for patients for whom the treatment goal is immediate abstinence.

Opioid administration

In an emergency situation when opioids must be administered to a patient taking SELINCRO, the amount of opioid required to obtain the desired effect may be greater than usual. The patient should be closely monitored for symptoms of respiratory depression as a result of the opioid administration and for other adverse reactions.

If opioids are needed in an emergency, the dose must always be titrated individually. If unusually large doses are required, close observation is necessary.

SELINCRO should be temporarily discontinued for 1 week prior to the anticipated use of opioids, for example, if opioid analgesics might be used during elective surgery.

The prescriber should advise patients that it is important to inform their health care professional of last SELINCRO intake if opioid use becomes necessary.

Caution should be exercised when using medicinal products containing opioids (for example, cough medicines, opioid analgesics [see INTERACTIONS WITH OTHER MEDICINES]).

Comorbidity

Psychiatric disorders

Psychiatric effects were reported in clinical studies (see ADVERSE EFFECTS). If patients develop psychiatric symptoms that are not associated with treatment initiation of SELINCRO, and/or that are not transient, the prescriber should consider alternative causes of the symptoms and assess the need for continuing treatment with SELINCRO.

SELINCRO has not been investigated in patients with unstable psychiatric disease. Caution should be exercised if SELINCRO is prescribed to patients with current psychiatric comorbidity.

Seizure disorders

There is limited experience in patients with a history of seizure disorders, including alcohol withdrawal seizures.

Caution is advised if treatment aimed at reduction of alcohol consumption is started in such patients.

Renal or hepatic impairment

SELINCRO is extensively metabolised by the liver and excreted predominantly in the urine. Therefore, caution should be exercised when prescribing SELINCRO to patients with mild or moderate hepatic or mild or moderate renal impairment, for example, by more frequent monitoring.

Caution should be exercised when prescribing SELINCRO to patients with elevated ALAT or ASAT (>3 times ULN) as these patients were excluded from the clinical development programme.

Others

Caution is advised if SELINCRO is co-administered with a potent UGT2B7 inhibitor (see INTERACTIONS WITH OTHER MEDICINES).

Lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Effects on fertility

There were no effects on fertility, mating, litter parameters or sperm parameters when rats were treated with nalmefene prior to and during mating and in early pregnancy at oral doses up to 200 mg/kg/day which achieved exposure (plasma C_{max}) at least 60 times that at the recommended human dose.

Use in pregnancy (Category B3)

There are limited data (fewer than 300 pregnancy outcomes) from the use of nalmefene in pregnant women.

SELINCRO is not recommended during pregnancy.

Nalmefene and/or its metabolites cross the placenta in pregnant rats. No teratogenic effects on fetuses were observed when nalmefene was administered to rats and rabbits during the period of organogenesis at oral doses up to 200 mg/kg/day, with respective estimated exposures (plasma AUC) of about 24 and 9 times that at the recommended human dose. In the rabbit study, reduced fetal weights and delayed ossification were observed at 200 mg/kg/day, while in the rat study, no adverse effects on fetuses were observed. The AUC at the no observable adverse effect level (NOAEL) for these effects in rabbits was below the human exposure at the recommended clinical dose.

When nalmefene was administered to rats at oral doses up to 100 mg/kg/day over the final 5-6 days of gestation and during lactation, a small decrease in post-natal viability of pups was observed at 100 mg/kg/day . This dose was maternotoxic.

Use in lactation

Nalmefene/nalmefene metabolites were excreted in the milk of lactating rats. It is unknown whether nalmefene is excreted in human milk.
A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from SELINCRO therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to the woman.

Paediatric Use

SELINCRO is not recommended for use in children and adolescents <18 years of age.

Elderly patients (≥65 years of age)

Limited clinical data are available on the use of SELINCRO in patients ≥65 years of age with alcohol use disorder.

Caution should be exercised when prescribing SELINCRO to patients ≥65 years of age (see DOSAGE & ADMINISTRATION and PHARMACOLOGY - Special populations).

Genotoxicity

Nalmefene was not genotoxic in two bacterial reverse mutation assays and a forward mutation test in mouse lymphoma cells in vitro, or in a mouse micronucleus test or a rat cytogenetics assay in vivo. In a chromosome aberration assay in human lymphocytes in vitro, nalmefene was negative in the presence of metabolic activation but positive in the absence of metabolic activation. A weight of evidence approach suggests that nalmefene does not have genotoxic potential.

Carcinogenicity

Long term carcinogenicity studies were conducted in mice (80 weeks) and rats (104 weeks) at dietary doses up to 100 mg/kg/day in both species. Estimated exposure achieved in the mouse and rat studies at 100 mg/kg/day (based on plasma AUC) was about 3 and 1.5 times, respectively, that expected at the recommended human dose. No oncogenic responses to nalmefene treatment were observed.

Effects on ability to drive and use machines

The effects of nalmefene on the ability to drive and use machines have not been studied.

SELINCRO may cause adverse reactions such as nausea, dizziness, insomnia, and headache. The majority of these reactions were mild or moderate, associated with treatment initiation, and of short duration.

SELINCRO has no or negligible influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

No *in vivo* drug-drug interaction studies have been conducted.

Co-administration with medicinal products that are potent inhibitors of the UGT2B7 enzyme (for example, diclofenac, fluconazole, medroxyprogesterone acetate, meclofenamic acid) may significantly increase exposure to nalmefene (see

PRECAUTIONS). Conversely, concomitant administration with a UGT inducer (for example, dexamethasone, phenobarbitone, rifampicin, omeprazole) may potentially lead to subtherapeutic nalmefene plasma concentrations.

Based on *in vitro* studies, nalmefene would appear to be neither a substrate nor an inhibitor of human efflux transporters, MDR1, BCRP or MRP2, nor an inhibitor of BSEP; and neither a substrate nor inhibitor of human uptake transporters, OATP1B1, OATP1B3 or OCT1, nor an inhibitor of OCT2, OAT1 or OAT3. Drug interactions with nalmefene via these transporters are therefore unlikely.

If SELINCRO is taken concomitantly with opioid agonists (for example, certain types of cough and cold medicinal products, certain antidiarrhoeal medicinal products, and opioid analgesics), the patient may not benefit from the opioid agonist.

There is no clinically relevant pharmacokinetic drug-drug interaction between nalmefene and alcohol. There seems to be a small impairment in cognitive and psychomotor performance after administration of nalmefene. However, the effect of nalmefene and alcohol in combination did not exceed the sum of the effects of each substance when taken alone.

Simultaneous intake of alcohol and SELINCRO does not prevent the intoxicating effects of alcohol.

ADVERSE EFFECTS

Summary of the safety profile

More than 3,000 patients have been exposed to nalmefene in clinical studies. Overall, the safety profile appears consistent across all the clinical studies conducted.

The incidences of treatment-emergent adverse events (TEAEs) were calculated based on three randomised, double-blind, placebo-controlled studies in patients with alcohol dependence (Alcohol Dependence Pool - 1,144 patients exposed to SELINCRO as-needed and 797 exposed to placebo as-needed – See CLINICAL TRIALS).

The TEAEs with the highest incidence in the SELINCRO group were nausea, dizziness, insomnia, and headache. The majority of these events were mild or moderate, associated with treatment initiation and of short duration. A total of 14% of patients in the SELINCRO group and 9% of patients in the placebo group had severe TEAEs; the severe TEAEs with an incidence $\geq$1% in the SELINCRO group were nausea, dizziness, insomnia, headache, and vomiting.

The clinically relevant, common and very common TEAEs that occurred in the three phase 3 clinical studies are described in Table 4. The TEAEs included are those with an incidence

≥ 1% in the SELINCRO group and for which the incidence was greater than that in the placebo group.

Confusional state and, rarely, hallucinations and dissociation were reported in the clinical development programme for nalmefene. The majority of these events were mild or moderate, associated with treatment initiation, and of short duration (a few hours to a few days). Most of these adverse events resolved during continued treatment and did not recur upon repeated administration. While these events were generally short-lasting, they could represent alcoholic psychosis, alcohol withdrawal syndrome, or comorbid psychiatric disease.

The overall incidence of TEAEs was 63% in the placebo group and 75% in the SELINCRO group.

Table 4: Clinically Relevant Common and Very Common[1] Treatment-Emergent Adverse Events (TEAEs) in Clinical Studies[2] of Alcohol Dependence

BODY SYSTEM **Adverse event**	**Percentage (%) of patients reporting TEAEs** **TEAE Incidence (%)**	
	Placebo (n=797)	**SELINCRO** (n=1144)
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	1.1	4.9
PSYCHIATRIC DISORDERS		
Confusional state	0.3	1.2
Insomnia	5.4	13.4
Libido decreased (including loss of libido)[3]	0.4	1.5
Restlessness	0.3	1.1
Sleep disorder	0.6	3.3
NERVOUS SYSTEM DISORDERS		
Disturbance in attention	0.5	2.6
Dizziness	5.5	18.2
Headache	8.3	12.3
Hypoaesthesia	0.1	1.3
Paraesthesia	0.3	1.7
Somnolence	2.9	5.2
Tremor	1.4	3.5
CARDIAC DISORDERS		
Palpitations	0.1	1.1
Tachycardia	1.0	2.9
GASTROINTESTINAL DISORDERS		
Dry mouth	1.5	3.0
Nausea	5.9	22.1
Vomiting	2.3	8.7
SKIN AND SUBCUTANEOUS TISSUE DISORDER		
Hyperhidrosis	1.0	4.3
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		

BODY SYSTEM **Adverse event**	**Percentage (%) of patients reporting TEAEs** **TEAE Incidence (%)**	
	Placebo (n=797)	**SELINCRO** (n=1144)
Muscle spasms	-	1.7
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS		
Asthenia	0.6	2.9
Fatigue	4.6	8.3
Feeling abnormal	0.1	1.5
Malaise	0.3	2.0
INVESTIGATIONS		
Weight decreased	0.4	1.4

[1] Common: ≥1/100 to <1/10; Very Common: ≥1/10

[2] Clinical Studies: Study 1 (12014A), Study 2 (12023A) and an additional 1 year study in alcohol dependence including 665 patients (12013A)

[3] The combination of these terms is considered clinically relevant and therefore included in Table 4

It was also observed in the clinical studies that during the second and subsequent months of treatment, the incidence and prevalence values for nausea, insomnia, vomiting, fatigue and somnolence were consistently and considerably lower than during the first month of treatment.

Alcohol withdrawal syndrome was reported in 0.7% of subjects given nalmefene and 0.1% given placebo.

DOSAGE AND ADMINISTRATION

SELINCRO may be initiated in patients who have been provided with psychosocial intervention for at least 2 weeks but continue to consume >60 g alcohol daily (men) or >40 g alcohol daily (women).

At an initial visit, the patient's clinical status, alcohol use disorder, and level of alcohol consumption (based on patient reporting) should be evaluated. Thereafter, the patient should be asked to record his or her alcohol consumption for approximately two weeks.

At the next visit, Selincro may be initiated in patients who continued to have a high DRL (see INDICATION) over this two-week period, in conjunction with psychosocial intervention focused on treatment adherence and reducing alcohol consumption.

During pivotal studies the greatest reduction in alcohol consumption was observed within the first 4 weeks.

The patient's response to treatment and the need for continued pharmacotherapy should be evaluated on a regular basis (e.g. monthly). The physician should continue to assess the patient's progress in reducing alcohol consumption, overall functioning, treatment

adherence, and any potential side effects. Caution is advised if SELINCRO is prescribed for more than 24 weeks.

SELINCRO is to be taken as-needed: on each day the patient perceives a risk of drinking alcohol; one tablet should be taken, preferably 1-2 hours prior to the anticipated time of drinking. If the patient has started drinking alcohol without taking SELINCRO, the patient should take one tablet as soon as possible.

The maximum dose of SELINCRO is one tablet per day. SELINCRO can be taken with or without food (see PHARMACOLOGY).

Method of administration:

SELINCRO is for oral use.
The film-coated tablet should be swallowed whole.
The film-coated tablet should not be divided or crushed because nalmefene may cause skin sensitisation when in direct contact with the skin.

Elderly (≥65 years of age)

No dose adjustment is recommended for this patient population (see PRECAUTIONS and PHARMACOLOGY).

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (see PRECAUTIONS and PHARMACOLOGY).

Hepatic impairment

No dose adjustment is recommended for patients with mild or moderate hepatic impairment (see PRECAUTIONS and PHARMACOLOGY).

Paediatric population

The safety and efficacy of SELINCRO in children and adolescents <18 years of age have not been established. No data are available.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre (Tel: 13 11 26 for Australia).

In a study in patients diagnosed with pathological gambling, doses of nalmefene up to 90 mg/day for 16 weeks were investigated. In a study in patients with interstitial cystitis, 20 patients received 108 mg/day of nalmefene for more than 2 years. Intake of a single

dose of 450 mg nalmefene has been reported without changes in blood pressure, heart rate, respiration rate, or body temperature.

No unusual pattern of adverse reactions was observed in these settings, but experience is limited.

Management of an overdose should be observational and symptomatic.

PRESENTATION AND STORAGE CONDITIONS

Film-coated tablet: White, oval, biconvex, 6.0 x 8.75 mm film-coated tablet engraved with "S" on one side
Pack: Clear PVC/PVdC-aluminium blisters in cardboard boxes
Pack sizes: 7, 14, 28, 42, and 98 film-coated tablets
Not all pack sizes may be marketed.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Lundbeck Australia Pty Ltd
Ground Floor
1 Innovation Road
North Ryde NSW 2113
Australia

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

17 June 2015