ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Selincro 18 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 18.06 mg nalmefene (as hydrochloride dihydrate).

Excipient with known effect

Each film-coated tablet contains 60.68 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
White, oval, biconvex, 6.0 x 8.75 mm film-coated tablet engraved with “S” on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high drinking risk level (DRL) [see section 5.1], without physical withdrawal symptoms and who do not require immediate detoxification.

Selincro should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.

Selincro should be initiated only in patients who continue to have a high DRL two weeks after initial assessment.

4.2 Posology and method of administration

Posology

At an initial visit, the patient’s clinical status, alcohol dependence, 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 section 5.1) over this two-week period, in conjunction with psychosocial intervention focused on treatment adherence and reducing alcohol consumption.

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 section 5.2).

During pivotal trials the greatest improvement 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

(for example, monthly) basis (see section 5.1). The physician should continue to assess the patient's progress in reducing alcohol consumption, overall functioning, treatment adherence, and any potential side effects. Clinical data for the use of Selincro under randomised controlled conditions are available for a period of 6 to 12 months. Caution is advised if Selincro is prescribed for more than 1 year.

Special populations

Elderly (≥65 years of age)
No dose adjustment is recommended for this patient population (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is recommended for patients with mild or moderate renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild or moderate hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of Selincro in children and adolescents <18 years of age have not been established. No data are available (see section 5.1).

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 (see section 5.3).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients taking opioid agonists (such as opioid analgesics, opioids for substitution therapy with opioid agonists (e.g. methadone) or partial agonists (e.g. buprenorphine)) (see section 4.4).

Patients with current or recent opioid addiction.

Patients with acute symptoms of opioid withdrawal.

Patients for whom recent use of opioids is suspected.

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).

4.4 Special warnings and precautions for use

Selincro is not for patients for whom the treatment goal is immediate abstinence. Reduction of alcohol consumption is an intermediate goal on the way to 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 section 4.5)).

Comorbidity

Psychiatric disorders
Psychiatric effects were reported in clinical studies (see section 4.8). If patients develop psychiatric symptoms that are not associated with treatment initiation with 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 such as major depressive disorder.

The increased suicidal risk in alcohol and substances abusers, with or without accompanying depression, is not reduced by the intake of nalmefene.

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.

Elderly patients (≥65 years of age)

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

Caution should be exercised when prescribing Selincro to patients ≥65 years of age (see sections 4.2 and 5.2).

Others

Caution is advised if Selincro is co-administered with a potent UGT2B7 inhibitor (see section 4.5).

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Based on *in vitro* studies, no clinically relevant interactions between nalmefene, or its metabolites, and concomitantly administered medicinal products metabolised by the most common CYP450 and UGT enzymes or membrane transporters are anticipated. Co-administration with medicinal products that are potent inhibitors of the UGT2B7 enzyme (for example, diclofenac, fluconazole, medroxyprogesterone acetate, meclofenamic acid) may significantly increase the exposure to nalmefene. This is unlikely to present a problem with occasional use, but if long-term concurrent treatment with a potent UGT2B7 inhibitor is initiated, a potential for an increase in nalmefene exposure cannot be excluded (see section 4.4). Conversely, concomitant administration with a UGT inducer (for example, dexamethasone, phenobarbital, rifampicin, omeprazole) may potentially lead to subtherapeutic nalmefene plasma concentrations.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data (fewer than 300 pregnancy outcomes) from the use of nalmefene in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3).

Selincro is not recommended during pregnancy.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of nalmefene/metabolites in milk (see section 5.3). 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.

Fertility

In fertility studies in rats, no effects were observed for nalmefene on fertility, mating, pregnancy, or sperm parameters.

4.7 Effects on ability to drive and use machines

Adverse reactions such as disturbance in attention, visual impairment, feeling abnormal, nausea, dizziness, somnolence, insomnia, and headache may occur following administration of nalmefene (see section 4.8). The majority of these reactions were mild or moderate, associated with treatment initiation, and of short duration.

Consequently, Selincro may have minor to moderate influence on the ability to drive and use machines and patients should exercise caution particular when starting treatment with Selincro.

4.8 Undesirable effects

Summary of the safety profile

The frequencies of the adverse reactions in Table 1 were calculated based on three randomised, double-blind, placebo-controlled studies in patients with alcohol dependence.

The most common adverse reactions were nausea, dizziness, insomnia, and headache. The majority of these reactions were mild or moderate, associated with treatment initiation, and of short duration.

Confusional state and, rarely, hallucinations and dissociation were reported in the clinical studies. The majority of these reactions were mild or moderate, associated with treatment initiation, and of short duration (a few hours to a few days). Most of these adverse reactions 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.

Tabulated list of adverse reactions

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data).

Table 1. Frequencies of adverse reactions

System Organ Class	*Frequency*	*Adverse Reaction*
Metabolism and nutrition disorders	Common	Decreased appetite
Psychiatric disorders	Very common	Insomnia
	Common	Sleep disorder
		Confusional state
		Restlessness
		Libido decreased (including loss of libido)
	Uncommon	Hallucination (including hallucination auditory, hallucination tactile, hallucination visual, and somatic hallucination)
		Dissociation
Nervous system disorders	Very Common	Dizziness
		Headache
	Common	Somnolence
		Tremor
		Disturbance in attention
		Paraesthesia
		Hypoaesthesia
Eye disorders	Not known	Visual impairment (mostly transient)
Cardiac disorders	Common	Tachycardia
		Palpitations
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
		Dry mouth
		Diarrhoea
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Not known	Angioedema
		Urticaria
		Pruritus
		Rash
		Erythema
Musculoskeletal and connective tissue disorders	Common	Muscle spasms
	Not known	Myalgia
Reproductive system and breast disorder	Not known	Priapism
General disorders and administration site conditions	Common	Fatigue
		Asthenia
		Malaise
		Feeling abnormal
Investigations	Common	Weight decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, drugs used in alcohol dependence;
ATC code: N07BB05

Mechanism of action

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.

Data from the nonclinical studies, the clinical studies, and the literature do not suggest any form of dependence or abuse potential with Selincro.

Clinical efficacy and safety

The efficacy of Selincro in reducing alcohol consumption in patients with alcohol dependence (DSM-IV) was evaluated in two efficacy studies. 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 DRL (alcohol consumption >60 g/day for men and >40 g/day for women according to the WHO DRLs of alcohol consumption) 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. The efficacy of Selincro was also evaluated in a randomised, double-blind, parallel-group, placebo-controlled 1-year study. Overall, the studies included 1,941 patients, 1,144 of whom were treated with Selincro 18 mg as-needed.

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 (n=579), and 2 (n=655), 18%, and 33%, of the total population, respectively, considerably reduced their alcohol consumption in the period between screening and randomisation. As concerns the patients with high or very high DRL at baseline, 35% of patients experienced improvement due to non-pharmacological effects in the period between the initial visit (screening) and randomisation. At randomisation, these patients consumed such a small amount of alcohol that there was little room for further improvement (floor effect). 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.

The clinical efficacy and the clinical relevance of Selincro were analysed in patients with a high or very high DRL at screening and randomisation. At baseline, the patients had, on average, 23 HDDs per month (11% of patients had fewer than 14 HDDs per month) and consumed 106 g/day. The majority of the patients had low (55% had a score of 0-13) or intermediate (36% had a score of 14-21) alcohol dependence according to the Alcohol Dependence Scale.

Post-hoc efficacy analysis in 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). For HDDs there were 23 days/month at baseline in the Selincro group (n=171) and 23 days/month at baseline in the placebo group (n=167). For the patients who continued in the study and provided efficacy data at Month 6, the number of HDDs was 9 days/month in the Selincro group (n=85) and 14 days/month in the placebo group (n=114). The TAC was 102 g/day at baseline in the Selincro group (n=171) and 99 g/day at baseline in the placebo group (n=167). For the patients who continued in the study and provided efficacy data at Month 6, the TAC was 40 g/day in the Selincro-group (n=85) and 57 g/day in the placebo group (n=114).

In Study 2, the proportion of patients who withdrew was higher in the Selincro group than in the placebo group (30% versus 28%, respectively). For HDDs there were 23 days/month at baseline in the Selincro group (n=148) and 22 days/month at baseline in the placebo group (n=155). For the patients who continued in the study and provided efficacy data at Month 6, the number of HDDs was 10 days/month in the Selincro group (n=103) and 12 days/month in the placebo group (n=111). The TAC was 113 g/day at baseline in the Selincro group (n=148) and 108 g/day at baseline in the placebo group (n=155). For the patients who continued in the study and provided efficacy data at Month 6, the TAC was 44 g/day in the Selincro group (n=103) and 52 g/day in the placebo group (n=111).

Responder analyses of the pooled data from the two studies are provided in Table 2.

Table 2. Pooled Responder Analysis Results in Patients with a High or Very High DRL at screening and Randomisation

Response[a]	Placebo	Nalmefene	Odds Ratio (95% CI)	p-value
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 treats patients who withdrew as non-responder
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)

Limited data are available for Selincro in the 1-month run-out period.

1 year study
This study comprised a total of 665 patients. 52% of these patients had a high or very high DRL at baseline; of these, 52% (representing 27% of the total population) continued to have a high or very high DRL at randomisation. In this post-hoc target population, more patients receiving nalmefene

discontinued (45%) as compared to those receiving placebo (31%). For HDDs there were 19 days/month at baseline in the Selincro-group (n=141) and19 days/month at baseline in the placebo group (n=42). For the patients who continued in the study and provided efficacy data at 1 year, the number of HDDs was 5 days/month in the Selincro group (n=78) and 10 days/month in the placebo group (n= 29). The TAC was 100 g/day at baseline in the Selincro group (n=141) and 101 g/day at baseline in the placebo group (n=42). For the patients who continued in the study and provided efficacy data at 1 year, the TAC was 24 g/day in the Selincro group (n=78) and 47 g/day in the placebo group (n=29).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Selincro in all subsets of the paediatric population for the treatment of alcohol dependence (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Nalmefene is rapidly absorbed after a single oral administration of 18.06 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 is 41%. 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 (V_d/F) is approximately 3200 l.
Occupancy data obtained in a PET study after single and repeated daily dosing with 18.06 mg nalmefene show 94% to 100% receptor occupancy within 3 hours after dosing, which suggests that nalmefene readily crosses the blood-brain barrier.

Biotransformation

Following oral administration, nalmefene undergoes extensive, rapid metabolism to the major metabolite nalmefene 3-O-glucuronide, with the UGT2B7 enzyme being primarily responsible for the conversion, and with the UGT1A3 and UGT1A8 enzymes as minor contributors. 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 not considered to contribute with significant pharmacological effect on the opioid receptors in humans, except for nalmefene 3-O-sulphate, which has a potency comparable to that of nalmefene. However, nalmefene 3-O-sulphate is present in concentrations less than 10% of that of nalmefene and thus considered highly unlikely to be a major contributor to the pharmacological effect of nalmefene.

Elimination

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 any 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.

Renal impairment

Administration of a single oral dose of nalmefene 18.06 mg to patients with mild, moderate or severe renal impairment, classified using the estimated glomerular filtration rate, resulted in an increased exposure to nalmefene relative to that in healthy subjects. For patients with mild, moderate or severe renal impairment the AUC for nalmefene was 1.1 times, 1.4 times and 2.4 times higher, respectively. Further, the C_{max} and elimination half-life for nalmefene was up to 1.6 times higher in patients with severe renal impairment. No clinically relevant changes were seen in t_{max} for any of the groups. For the inactive major metabolite nalmefene 3-O-glucuronide, the AUC and C_{max} were up to 5.1 times and 1.8 times higher in patients with severe renal impairment, respectively (see sections 4.3 and 4.4).

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 sections 4.3 and 4.4).

Elderly

No specific study with oral dosing has been conducted in patients ≥65 years of age. A study with IV administration suggested that there were no relevant changes in the pharmacokinetics in the elderly as compared to non-elderly adults (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Nalmefene was shown to have skin sensitisation potential in the Local Lymph Node Assay in mice after topical application.

Studies in animals do not indicate direct harmful effects with respect to fertility, pregnancy, embryonic/foetal development, parturition, or postnatal development.

In a rabbit embryo-foetal developmental toxicity study, effects on foetuses in terms of reduced foetal weight and delayed ossification, but no major abnormalities were seen. The AUC at the no observed adverse effect level (NOAEL) for these effects was below the human exposure at the recommended clinical dose.
An increase in still-born pups and decrease in post-natal viability of pups was observed in pre-postnatal toxicity studies in rats. This effect was considered to be an indirect effect related to toxicity to the dams.

Studies in rats have shown excretion of nalmefene or its metabolites in milk.

The nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, or carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Lactose, anhydrous
Crospovidone, type A
Magnesium stearate

Tablet coating

Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister: Clear PVC/PVdC-aluminium blisters in cardboard boxes
Pack sizes of 7, 14, 28, 42, 49 and 98 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/815/001 7 tablets
EU/1/12/815/002 14 tablets
EU/1/12/815/003 28 tablets
EU/1/12/815/004 42 tablets
EU/1/12/815/005 98 tablets
EU/1/12/815/006 49 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 February 2013
Date of latest renewal: 10 November 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release
H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby
Denmark

Elaiapharm
2881, Route des Crêtes
Z.I. Les Bouillides
Sophia Antipolis
06560 Valbonne
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Selincro 18 mg film-coated tablets
nalmefene

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 18.06 mg nalmefene (as hydrochloride dihydrate).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 film-coated tablets
14 film-coated tablets
28 film-coated tablets
42 film-coated tablets
49 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S
Ottiliavej 9
DK-2500 Valby
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/815/001 7 tablets
EU/1/12/815/002 14 tablets
EU/1/12/815/003 28 tablets
EU/1/12/815/004 42 tablets
EU/1/12/815/005 98 tablets
EU/1/12/815/006 49 tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Selincro

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Selincro 18 mg tablet
nalmefene

2. NAME OF THE MARKETING AUTHORISATION HOLDER

H. Lundbeck A/S

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Selincro 18 mg film-coated tablets
nalmefene

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Selincro is and what it is used for

Selincro contains the active substance nalmefene.

Selincro is used for the reduction of alcohol consumption in adult patients with alcohol dependence who still have a high level of alcohol consumption 2 weeks after the first consultation with their doctor.

Alcohol dependence occurs when a person has a physical or psychological dependence on the consumption of alcohol.

A high level of alcohol consumption is defined as drinking more than 60 g of pure alcohol per day for men and more than 40 g of pure alcohol per day for women. For example, a bottle of wine (750 ml; 12% alcohol by volume) contains approximately 70 g alcohol and a bottle of beer (330 ml; 5% alcohol by volume) contains approximately 13 g alcohol.

Your doctor has prescribed Selincro because you were not able to reduce your alcohol consumption on your own. Your doctor will provide you with counselling to help you keep to your treatment and thereby reduce your alcohol consumption.

Selincro works by affecting processes in the brain that are responsible for your urge to continue drinking.

A high level of alcohol consumption is associated with an increased risk of health and social problems. Selincro can help you reduce the amount of alcohol you drink, and keep the reduced level of alcohol consumption.

2. What you need to know before you take Selincro

Do not take Selincro:

- if you are allergic to nalmefene or any of the other ingredients of this medicine (listed in section 6)
- if you are taking medicines containing opioids, for example, methadone or buprenorphine or pain killers (such as morphine, oxycodone or other opioids)
- if you are or have recently been dependent on opioids. You may experience acute opioid withdrawal symptoms (such as feeling sick, vomiting, shakiness, sweating and anxiety)
- if you experience, or suspect you are experiencing opioid withdrawal symptoms
- if your liver or kidney function is poor
- if you are experiencing or have recently experienced several alcohol withdrawal symptoms (such as seeing, hearing or sensing things that are not there, seizures and shakiness)

Warnings and precautions

Talk to your doctor or pharmacist before taking Selincro. Inform your doctor about any other diseases you may have, for example, depression, seizure, liver or kidney disease.

If you and your doctor have decided that your immediate goal is abstinence (not drinking any alcohol), you should not take Selincro because Selincro is indicated for reduction of alcohol consumption.

If you require emergency medical attention, tell your doctor that you are taking Selincro. Your use of Selincro may affect your doctor's choice of emergency treatment.

If you are going to have a surgical procedure, talk to your doctor at least 1 week before the procedure. You may need to stop taking Selincro temporarily.

If you feel detached from yourself, see or hear things that are not there, and this continues to recur for more than a few days, stop taking Selincro and talk to your doctor.

The increased suicidal risk in alcohol and substances abusers, with or without accompanying depression, is not reduced by the intake of nalmefene.

If you are 65 years old or above, talk to your doctor or pharmacist before taking Selincro.

Children and adolescents

Selincro should not be used in children or adolescents below the age of 18 years because Selincro has not been tested in this age group.

Other medicines and Selincro

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Caution should be excercised when taking medicines such as diclofenac (antiinflammatory medicine used to treat, for example, muscle pain), fluconazole (medicine used to treat diseases caused by some types of fungus), omeprazole (medicine used to block the production of acid in the stomach), or rifampicin (antibiotic used to treat diseases caused by some types of bacteria) together with Selincro.

If you take medicines containing opioids, the effects of these medicines will be reduced, or the medicines may not work at all if you take them together with Selincro. These medicines include certain types of cough and cold medicines, certain medicines for diarrhoea and strong pain killers.

Selincro with food and alcohol

Selincro does not prevent the intoxicating effects of alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known if Selincro is safe to use during pregnancy and breast-feeding.

Selincro is not recommended if you are pregnant.

If you are breast-feeding, you and your doctor should make a decision whether to discontinue breast-feeding or to discontinue Selincro therapy, taking into account the benefit of breast-feeding to the child and the benefit of therapy to you.

Driving and using machines

Side effects such as disturbance in attention, visual impairment, feeling abnormal, nausea, dizziness, somnolence, insomnia, and headache may occur when beginning Selincro treatment. The majority of these reactions were mild or moderate, occurred at the beginning of treatment and lasted for a few hours to a few days. These side effects may affect your skills when driving or doing anything that requires you to be alert, including operating machinery.

Selincro contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Selincro

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- The recommended dose is one tablet on days when you think there is a risk you will drink alcohol.
- The maximum dose is one tablet per day.

How and when to take

- Selincro is for oral use.
- You should take the tablet 1-2 hours before you start drinking alcohol.
- Swallow the tablet whole, do not crush or divide the tablet because Selincro may cause skin sensitisation when in direct contact with the skin.
- You can take Selincro with or without food.
- You can expect to be able to reduce your alcohol consumption within the first month after you start treatment with Selincro.
- Your doctor will follow up with you on a regular basis, for example, monthly after you start treatment with Selincro; the actual frequency will depend on your progress. Together you will decide how to continue.

If you take more Selincro than you should

If you believe you have taken too many Selincro tablets, contact your doctor or pharmacist.

If you forget to take Selincro

If you have started drinking alcohol without taking Selincro, take one tablet as soon as possible.

If you stop taking Selincro

After you stop treatment with Selincro, you may be less sensitive to the effects of medicines containing opioids for a few days.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects of seeing, hearing or sensing things that are not there or feeling detached from oneself are uncommon (may affect up to 1 in 100 people). If you experience any of these side effects, consult your doctor.

The side effects reported with Selincro were mainly mild or moderate, occurred at the beginning of treatment and lasted for a few hours to a few days.
If you continue treatment with Selincro, or start again after a break in treatment, you will probably not have side effects.
In some cases, it may be difficult for you to distinguish side effects from the symptoms you may feel when you reduce your alcohol consumption.

The following side effects have been reported with Selincro:

Very common (may affect more than 1 in 10 people)
- feeling sick
- dizziness
- inability to sleep
- headache

Common (may affect up to 1 in 10 people)
- loss of appetite
- difficulty sleeping, confusion, feeling restless, reduced sex drive
- drowsiness, body twitches, feeling less alert, peculiar sensation in the skin like pins and needles, reduced sense of touch
- racing heart, a sensation of a rapid, forceful, or irregular beating of the heart
- vomiting, dry mouth, diarrhoea
- excessive sweating
- muscle spasms
- feeling of exhaustion, weakness, discomfort or uneasiness, feeling strange
- weight loss

Other side effects (cannot be estimated from the available data)
- visual impairment (mostly transient)
- swelling of face, lips, tongue or throat
- hives
- itching

- rash
- redness of skin
- muscle pain
- prolonged erection (priapism)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Selincro

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date (EXP) that is printed on the blister and carton. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice defects in the tablets, such as chipped or broken tablets.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Selincro contains
- Each film-coated tablet contains 18.06 milligram nalmefene (as hydrochloride dihydrate).
- The other ingredients are:
  The tablet core: microcrystalline cellulose, anhydrous lactose, crospovidone (type A), magnesium stearate.
  The film-coating of the tablet contains: hypromellose, macrogol 400, titanium dioxide (E171).

What Selincro looks like and contents of the pack
Selincro is a white, oval, biconvex, film-coated tablet of 6.0 x 8.75 mm.
The tablet is engraved with 'S' on one side.

Selincro is available in packs of 7, 14, 28, 42, 49 or 98 tablets in blister cards.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.