תוכן עלון זה עודכן בהתאם להוראות משרד הבריאות, בתאריך ספטמבר 2017

## 1. NAME OF THE MEDICINAL PRODUCT

Selincro 18mg 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.

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.

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).

*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.

*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, Lapp 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

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

Adverse reactions such as disturbance in attention, feeling abnormal, nausea, dizziness, 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.
Consequentially, Selincro may influence the ability to drive and use machines and patients should exercise caution when starting treatment with Selincro.

## 4.8 Undesirable 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 frequencies of the adverse reactions in Table 1 were calculated based on three randomised, double-blind, placebo-controlled studies in patients with alcohol dependence (1,144 patients exposed to Selincro as-needed and 797 exposed to placebo as-needed).

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) |
| | Not known | 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 |
| Cardiac disorders | Common | Tachycardia |
| | | Palpitations |
| Gastrointestinal disorders | Very Common | Nausea |
| | Common | Vomiting |
| | | Dry mouth |
| | | Diarrhoea |
| Skin and subcutaneous tissue disorders | Common | Hyperhidrosis |
| Musculoskeletal and connective tissue disorders | Common | Muscle spasms |
| General disorders and administration site conditions | Common | Fatigue |
| | | Asthenia |
| | | Malaise |
| | | Feeling abnormal |
| Investigations | Common | Weight decreased |

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

### 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 in 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 (5 mPa.S)
Macrogol 400
Titanium dioxide (E171)

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

store below 30ºC

### 6.5 Nature and contents of container

Clear PVC/PVdC-aluminium blisters in cardboard boxes
Pack sizes of 7, 14, 28, 42, 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. Manufacturer

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

Licnese Holder:

LUNDBECK ISRAEL Ltd 4 DERECH HASHALOM , POB 7382, TEL AVIV

עלון זה נבדק ואושר ע״י משרד הבריאות בתאריך ספטמבר 2016