Availability of Serdolect® (sertindole) for a restricted indication and with special precautions with regard to the risk of QT prolongation

Dear Healthcare Professional,

Serdolect® was suspended from the European markets in 1998 following concerns over cardiac safety. In 2002, CHMP lifted this suspension. However, Serdolect® has only been available to patients that were included in clinical studies.

As of 2005, the CHMP has decided to lift this existing limitation of use. Serdolect® is now available under normal conditions of use in a restricted indication and with special precautions. This decision was reached following an overall assessment of benefit/risk, including preliminary information gained from a large ongoing study.

Restricted indication and ECG monitoring

Serdolect should only be prescribed to patients with schizophrenia. Due to cardiovascular safety concerns, **sertindole should only be prescribed for patients intolerant of at least one other antipsychotic agent.**

We would like to draw your attention to the enclosed Summary of Product Characteristics (SPC) and the contraindications for use. Summarised briefly these contraindications concern patients

- with clinically significant cardiovascular disease
- with congenital long QT syndrome, a family history of this disease, or known acquired QT interval prolongation
- receiving drugs known to significantly prolong the QT interval
- receiving drugs known to potently inhibit hepatic cytochrome P450 3A enzymes

In agreement with the CHMP and the Irish Medicines Board, Lundbeck has updated the SPC to strengthen the safeguards to be observed when using Serdolect. Because Serdolect prolongs the QT interval to a greater extent than some other antipsychotics, ECG monitoring is mandatory prior to and during treatment.

Instructions for ECG monitoring are provided in the enclosed SPC and are summarised as follows:

- ECG monitoring should be conducted at baseline, when reaching steady state after approximately 3 weeks or when reaching 16 mg and again after every 3 months of treatment
- During maintenance treatment, an ECG is required every 3 months
- An ECG is recommended after the addition, or increase of dosage, of concomitant medication that may increase the sertindole concentration

In addition we would like to draw your attention to the following:

- if a QT_c interval of more than 500 msec is observed during treatment with sertindole, treatment with sertindole should be **discontinued,** or
- when patients experience symptoms such as palpitations, convulsions, or syncope that could indicate the occurrence of arrhythmias, the prescriber should initiate urgent evaluation including an ECG.

In view of the increased risk of significant cardiovascular disease in the elderly:

- Serdolect® should only be used after careful consideration in patients above 65 years of age and a thorough cardiovascular examination is recommended prior to initiation of treatment with Serdolect® in this group of patients.

We trust this information will help you to follow the prescribing information for Serdolect® and optimise the treatment of your patient with schizophrenia and we would take this opportunity to request that you update your clinical teams with this important safety information also.

We encourage you to report any new case of suspected adverse reactions associated with Serdolect, either to Lundbeck directly at the address below or to the Irish Medicines Board in the usual way.

Sincerely,

Eithne Boyan
Managing Director
Lundbeck (Ireland) Limited

Address for Reporting Adverse Events:

Lundbeck (Ireland) Limited
7 Riverwalk
Citywest Business Campus
Dublin 24
Tel: + 353 1 4689800
Fax: + 353 1 4689850
Email: medinfo@lundbeck.com

1 Name of the Medicinal Product

Serdolect 4 mg, 12 mg, 16 mg and 20 mg film-coated tablets

2 Qualitative and quantitative composition

Each 4 mg tablet contains:	sertindole 4 mg
Each 12 mg tablet contains	sertindole 12 mg
Each 16 mg tablet contains	sertindole 16 mg
Each 20 mg tablet contains	sertindole 20 mg

For a full list of excipients see section 6.1.

3 Pharmaceutical form

Film-coated tablet

Description of tablets:
4 mg: Oval, yellow, biconvex, film-coated tablets marked with "S4" on one side.
12 mg: Oval, beige, biconvex, film-coated tablets marked with "S12" on one side.
16 mg: Oval, rose, biconvex, film-coated tablets marked with "S16" on one side.
20 mg: Oval, pink, biconvex, film-coated tablets marked with "S20" on one side.

4 Clinical Particulars

4.1 Therapeutic indications

Sertindole is indicated for the treatment of schizophrenia.

Due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antipsychotic agent.

Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.

4.2 Posology and method of administration

Sertindole is administered orally once daily with or without meals. In patients where sedation is required, a benzodiazepine may be co-administered.

Note: ECG monitoring is required before and during treatment with sertindole; see section 4.4.

Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.

Prescribing physicians should comply fully with the required safety measures: see sections 4.3 and 4.4.

Titration

All patients should be started on sertindole 4 mg/day. The dose should be increased by increments of 4 mg after 4-5 days on each dose until the optimal daily maintenance dose within the range of 12-20 mg is reached. Due to the α_1-blocking

activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period. A starting dose of 8 mg or a rapid increase in dose carries a significantly increased risk of postural hypotension.

Maintenance

Dependent on individual patient response, the dose may be increased to 20 mg/day. Only in exceptional cases should the maximum dose of 24 mg be considered, as clinical trials have not demonstrated consistently improved efficacy above 20 mg and QT prolongation may be increased at the upper end of the dose range.

The blood pressure of the patients should be monitored during titration and early maintenance treatment.

Elderly

A pharmacokinetic study showed no difference between young and elderly subjects. However, only limited clinical trial data exist for patients greater than 65 years of age. Treatment should only be initiated after a thorough cardiovascular examination. Slower titration and lower maintenance doses may be appropriate in elderly patients (see section 4.4).

Children and adolescents under the age of 18

Serdolect is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

Reduced renal function

Sertindole can be given at the usual dosage to patients with renal impairment (see section 4.3). The pharmacokinetics of sertindole is not affected by haemodialysis.

Reduced hepatic function

Patients with mild/moderate hepatic impairment require slower titration and a lower maintenance dose.

Re-titration of sertindole in patients for whom treatment has previously been discontinued

When restarting sertindole treatment in patients who have had an interval of less than one week without sertindole, re-titration of sertindole is not required and their maintenance dose can be re-introduced. Otherwise the recommended titration schedule should be followed. An ECG should be taken prior to re-titration of sertindole.

Switching from other antipsychotics

Treatment with sertindole can be initiated according to the recommended titration schedule concomitantly with cessation of other oral antipsychotics. For patients treated with depot antipsychotics, sertindole is initiated in place of the next depot injection.

4.3 Contra-indications

Hypersensitivity to sertindole or to any of the excipients.

Sertindole is contraindicated in patients with known uncorrected hypokalaemia and those with known uncorrected hypomagnesaemia.

Sertindole is contraindicated in patients with a history of clinically significant cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (<50 beats per minute).

Furthermore, sertindole should not be initiated in patients with congenital long QT syndrome or a family history of this disease, or in patients with known acquired QT interval prolongation (QTc above 450 msec in males and 470 msec in females).

Sertindole is contra-indicated in patients receiving drugs known to significantly prolong the QT interval. Relevant classes include:

- class Ia and III antiarrhythmics (eg. quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (eg. thioridazine)
- some macrolides (eg. erythromycin)
- some antihistamines (eg. terfenadine, astemizole)
- some quinolone antibiotics (eg. gatifloxacin, moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly increase QT interval (eg. cisapride, lithium) are also contraindicated.

Co-administration of sertindole is contraindicated with drugs known to potently inhibit hepatic cytochrome P450 3A enzymes (see section 4.5). Relevant classes include:

- systemic treatment with 'azole' antifungal agents (eg. ketoconazole, itraconazole)
- some macrolide antibiotics (eg. erythromycin, clarithromycin)
- HIV protease inhibitors (eg. indinavir)
- Some calcium channel blockers (eg. diltiazem, verapamil)

The above list is not exhaustive and other individual drugs known to potently inhibit CYP3A enzymes (eg. cimetidine) are also contraindicated.

Sertindole is contraindicated in patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Cardiovascular

Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QT_c interval in some drugs is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death. However, clinical and non-clinical data have been unable to confirm whether sertindole is more arrhythmogenic than other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.

Prescribing physicians should comply fully with the required safety measures.

ECG monitoring:

- ECG monitoring is mandatory prior to and during treatment with sertindole.
- Sertindole is contraindicated if a QT_c interval of more than 450 msec in males or 470 msec in females is observed at baseline.
- ECG monitoring should be conducted at baseline, upon reaching steady state after approximately 3 weeks or when reaching 16 mg and again after 3 months of treatment.
  During maintenance therapy an ECG is required every 3 months.
- During maintenance treatment, ECG measurements should take place prior to and after any increase in dose.

- An ECG is recommended after the addition or increase of dosage of concomitant medication that may increase the sertindole concentration (see section 4.5).
- If a QT_c interval of more than 500 msec is observed during treatment with sertindole, treatment with sertindole should be discontinued.
- For patients with symptoms such as palpitations, convulsions, or syncope that could indicate the occurrence of arrhythmias, the prescriber should initiate urgent evaluation, including an ECG.
- ECG monitoring is ideally conducted in the morning and the Bazett or Fridericia formulae for calculating the QT_c interval are preferred.

The risk of QT prolongation is increased in patients receiving concomitant treatment with drugs that prolong the QTc interval or drugs that inhibit sertindole metabolism (see section 4.3).

Baseline serum potassium and magnesium levels should be measured before commencing treatment with sertindole in patients at risk of significant electrolyte disturbances. Low serum potassium and magnesium should be corrected before proceeding with treatment. Monitoring of serum potassium is recommended for patients experiencing vomiting, diarrhoea, treatment with potassium-depleting diuretics, or other electrolyte disturbances.

Due to the α_1-blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period.

Antipsychotic drugs may inhibit the effects of dopamine agonists. Sertindole should be used cautiously in patients with Parkinson's disease.

Some SSRIs, like fluoxetine and paroxetine (potent CYP2D6 inhibitors), may increase the plasma levels of sertindole by a factor of 2 - 3. Sertindole should therefore only be used concomitantly with these drugs with extreme caution, and only if the potential benefit outweighs the risk. A lower maintenance dose of sertindole may be needed and careful ECG monitoring should be undertaken before and after any dose adjustment of these drugs (see section 4.5).

Sertindole should be used with caution in patients who are known to be poor CYP2D6 metabolisers (see Section 4.5).

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with sertindole. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Elderly patients

Sertindole is not approved for the treatment of dementia-related psychosis and/or behavioural disturbances and is not recommended for use in elderly patients with dementia.

An approximately 3-fold increased risk of cerebrovascular adverse events have been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Sertindole should be used with caution in patients with risk factors for stroke.

In view of the increased risk of significant cardiovascular disease in the elderly, sertindole should only be used with care in patients above 65 years of age. Treatment should only be initiated after a thorough cardiovascular examination.

Reduced hepatic function
Patients with mild/moderate hepatic dysfunction should be closely observed. Slower titration and a lower maintenance dose are recommended.

Tardive dyskinesia
Tardive dyskinesia is thought to be caused by dopamine receptor hypersensitivity in the basal ganglia as a result of chronic receptor blockade by antipsychotics. A low incidence (comparable to that of placebo) of extrapyramidal symptoms during treatment with sertindole has been seen in clinical studies. However, long-term treatment with antipsychotic compounds (especially at high dosages) is associated with the risk of tardive dyskinesia. If signs of tardive dyskinesia appear, dosage reduction or drug discontinuation should be considered.

Seizures
Sertindole should be used with caution in patients with a history of seizures.

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. The management of NMS should include immediate discontinuation of antipsychotic drugs.

Withdrawal
Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movements disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

Excipients
The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not receive this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Increases in the QT interval related to sertindole treatment may be exacerbated by the co-administration of other drugs known to significantly increase the QT interval. Co-administration of such drugs is therefore contraindicated (see section 4.3). Such an interaction may occur eg. between quinidine and sertindole. In addition to the effects on QT interval prolongation (see Section 4.3), CYP2D6 is markedly inhibited by quinidine.

Sertindole is extensively metabolised by the CYP2D6 and CYP3A isozymes of the cytochrome P450 system. CYP2D6 is polymorphic in the population and both isozymes can be inhibited by a variety of psychotropic and other drugs (see section 4.4).

CYP2D6
The plasma concentration of sertindole is increased by a factor of 2 - 3 in patients concurrently taking fluoxetine or paroxetine (potent CYP2D6 inhibitors), sertindole should therefore only be used concomitantly with these or other CYP2D6 inhibitors with extreme caution. A lower maintenance dose of sertindole may be needed and careful ECG monitoring should be undertaken before and after any dose adjustment of these drugs (see section 4.4).

CYP3A

Minor increases (<25%) in sertindole plasma concentrations have been noted for macrolide antibiotics (eg. erythromycin, a CYP3A inhibitor) and calcium channel antagonists (diltiazem, verapamil). However, the consequences could be greater in CYP2D6 poor metabolisers (since elimination of sertindole by both CYP2D6 and CYP3A would be affected). Therefore, because it is not possible to routinely identify patients who are poor metabolisers of CYP2D6, the concomitant administration of CYP3A inhibitors and sertindole is contraindicated, as this may lead to significant increases in sertindole levels (see section 4.3).

The metabolism of sertindole may be significantly enhanced by agents known to induce CYP isozymes, notably rifampicin, carbamazepine, phenytoin and phenobarbital, which can decrease the plasma concentrations of sertindole by a factor of 2 - 3. Reduced antipsychotic efficacy in patients receiving these drugs or other inducing agents may require the dose of sertindole to be adjusted to the upper dosage range.

4.6 Use during pregnancy and lactation

Pregnancy

The safety of sertindole for use during pregnancy has not been established.

Sertindole was not teratogenic in animal reproduction studies. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (see section 5.3).

Consequently, sertindole should not be used during pregnancy.

Lactation

Studies in nursing mothers have not been performed, however, it is expected that sertindole will be excreted in breast milk.

If treatment with sertindole is considered necessary, discontinuation of breast-feeding should be considered.

4.7 Effects on ability to drive and use machines

Sertindole is not sedative, however, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Side effects

In clinical trials, adverse events with an incidence greater than 1% associated with the use of sertindole and significantly different from placebo were (listed in order of decreasing frequency): rhinitis/nasal congestion, abnormal ejaculation (decreased ejaculatory volume), dizziness, dry mouth, postural hypotension, weight gain, peripheral oedema, dyspnoea, paraesthesia, and prolonged QT interval (see section 4.4).

Extrapyramidal Symptoms (EPS)

The incidences of patients treated with sertindole reporting EPS-related adverse events were similar to those of patients treated with placebo. In addition, in placebo-controlled clinical trials, the percentage of sertindole-treated patients requiring anti-EPS medication was indistinguishable from that of placebo-treated patients.

Some of the adverse drug reactions will appear at the beginning of treatment and disappear with continuous treatment, eg. postural hypotension.

The table below shows adverse reactions sorted by system organ class and frequency:

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <≤1/1000); very rare (≤1/10.000); not known (cannot be estimated from the available data).

Investigations	
Common	Weight gain, prolonged QT interval, red blood cells urine positive, white blood cells urine positive.
Cardiac disorders	
Common	Peripheral oedema
Uncommon	Torsade de Pointes (see section 4.4)
Nervous system disorders	
Common	Dizziness, paraesthesia
Uncommon	Syncope, convulsion, movement disorder (in particular tardive dyskinesia, see section 4.4)
Rare	Cases reported as Neuroleptic Malignant Syndrome (NMS) have been received in association with sertindole (see section 4.4)
Respiratory, thoracic and mediastinal disorders	
Very common	Rhinitis/nasal congestion
Common	Dyspnoea
Gastrointestinal disorders	
Common	Dry mouth
Metabolism and nutrition disorders	
Uncommon	Hyperglycaemia
Vascular disorders	
Common	Postural hypotension (see section 4.4)
Reproductive system and breast disorders	
Common	Abnormal ejaculation (decreased ejaculatory volume)

4.9 Overdose

Experience with sertindole in acute overdose is limited. Fatal cases have occurred. However, patients taking estimated dosages up to 840 mg have recovered without sequelae. Reported signs and symptoms of overdose were somnolence, slurred speech, tachycardia, hypotension, and transient prolongation of the QT_c interval. Cases of Torsade de Pointes have been observed, often in combination with other drugs known to induce TdP.

Treatment

In case of acute overdose, establishment of an airway and maintenance of adequate oxygenation should be ensured.

Continuous monitoring of ECG and vital signs should commence immediately. If the QT_c interval is prolonged, it is recommended that the patient be monitored until the QT_c interval has normalised. A half-life of sertindole of 2 to 4 days should be taken into account.

Intravenous access should be established and the administration of activated charcoal with laxative should be considered. The possibility of multiple drug involvement should be considered.

There is no specific antidote to sertindole, and it is not dialysable, therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, adrenaline and dopamine should be used with caution, since β stimulation combined with α_1 antagonism associated with sertindole may worsen hypotension.

If antiarrhythmic therapy is administered, agents such as quinidine, disopyramide and procainamide carry a theoretical hazard of QT interval-prolonging effects that might be additive to those of sertindole.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: limbic selective antipsychotics, ATC-code: N05A E 03

It has been proposed that the neuropharmacological profile of sertindole, as an antipsychotic drug, is derived from its selective inhibitory effect on mesolimbic dopaminergic neurons and is due to balanced inhibitory effects on central dopamine D_2 and serotonin $5HT_2$ receptors as well as on α_1-adrenergic receptors.

In animal pharmacology studies, sertindole inhibited spontaneously active dopamine neurons in the mesolimbic ventral tegmental area (VTA) with a selectivity ratio of more than 100 compared to dopamine neurons in substantia nigra pars compacta (SNC). Inhibition of SNC activity is thought to be involved in movement side effects (EPS) associated with many antipsychotic drugs.

Antipsychotic drugs are known to increase serum prolactin levels through dopamine blockade. The prolactin levels in patients receiving sertindole remained within normal limits, both in short-term studies and during long-term treatment (one year).

Sertindole has no effect on muscarinic and histaminic H_1 receptors. This is confirmed by the absence of anticholinergic and sedative effects related to those receptors.

5.2 Pharmacokinetic properties

Elimination of sertindole occurs via hepatic metabolism, with a mean terminal half-life of approximately 3 days. The clearance of sertindole decreases with multiple dosing to a mean around 14 l/h (females have approximately 20% lower apparent clearance than males, although lean-mass corrected clearances are comparable). Therefore, upon multiple dosing, accumulation is greater than predicted from a single dose, due to an increase in the systemic bioavailability. However, at steady state, clearance is dose independent and plasma concentrations are proportional to dose. There is moderate inter-subject variability in sertindole

pharmacokinetics, due to the polymorphism in the cytochrome P450 2D6 (CYP2D6). Patients who are deficient in this hepatic enzyme have sertindole clearances that are ½ to ⅓ of those who are CYP2D6 extensive metabolisers. These poor metabolisers (up to 10% of the population) will therefore have plasma levels 2-3 times the normal. Sertindole concentration is not predictive of therapeutic effect for an individual patient; thus, dosing individualisation is best achieved by assessment of therapeutic effect and tolerability.

Absorption

Sertindole is well absorbed with a t_{max} of sertindole after oral administration of approximately 10 hours. Different dose strengths are bioequivalent. Food and aluminium-magnesium antacids have no clinically significant effect on the rate or the extent of sertindole absorption.

Distribution

The apparent volume of distribution (V_β/F) of sertindole after multiple dosing is approximately 20 l/kg. Sertindole is about 99.5% bound to plasma proteins, primarily to albumin and α_1-acid glycoprotein. In patients treated with recommended doses, 90% of the measured concentrations are below 140 ng/ml (~320 nmol/l). Sertindole penetrates into red blood cells with a 1.0 blood/plasma ratio. Sertindole readily penetrates the blood-brain and placental barriers.

Metabolism

Two metabolites have been identified in human plasma: dehydrosertindole (oxidation of the imidazolidinone ring) and norsertindole (N-dealkylation). Concentrations of dehydrosertindole and norsertindole are approximately 80% and 40%, respectively, of the parent compound at steady state. Sertindole activity is primarily due to the parent drug and the metabolites do not appear to have significant pharmacological effects in humans.

Excretion

Sertindole and its metabolites are eliminated very slowly, with a total recovery of 50-60% of a radiolabelled oral dose 14 days after administration. Approximately 4% of the dose is excreted into the urine as parent drug plus metabolites of which less than 1% is present as parent drug. Faecal excretion is the major route of excretion and accounts for the rest of the parent drug and metabolites.

5.3 Preclinical safety data

QT prolongation on the ECG, possibly due to inhibition of the delayed rectifier potassium channel (I_{Kr}, HERG), has been observed in animal studies. However, sertindole shows absence of early after-depolarisations in cardiac rabbit and dog purkinje fibres. Early after-depolarisations are considered essential to trigger Torsade de Pointes. Sertindole did not induce Torsade de Pointes ventricular arrhythmias in atrio-ventricular node ablated rabbit hearts, despite experimental introduction of severe hypokalaemia (1.5 mmol) and bradycardia. However, the extrapolation of animal findings to humans with regard to QT prolongation and arrhythmia must be undertaken with caution as significant inter-species differences may exist.

The acute toxicity of sertindole is low. In chronic toxicity studies in the rat and dog (3-5 times clinical exposure), several effects were observed. These effects are in line with the pharmacological properties of the drug.

Animal reproduction studies have not given evidence of teratogenic effects. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (0.2 mg/kg/day), and at higher dosages, a decreased

pup survival in the early lactation period, reduced weight gain, and delayed development of pups in doses producing maternal toxicity.

Mating and fertility were affected in adult male rats at dosages of 0.14 mg/kg/day and above. The adult fertility impairment, which was reversible, was ascribed to the pharmacological profile of sertindole.

Sertindole was not toxic in a battery of *in vitro* and *in vivo* genotoxicity studies. Carcinogenicity studies conducted in the mouse and rat did not indicate any development of tumours relevant to the clinical use of sertindole.

6 Pharmaceutical particulars

6.1 List of Excipients

Tablet core
Maize starch
Lactose monohydrate
Hyprolose
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Tablet coating
Hypromellose
Titanium dioxide (E171)
Macrogol 400 and
4 mg : iron oxide yellow (E172)
12 mg: iron oxide yellow (E172) and iron oxide red (E172)
16 mg: iron oxide red (E172)
20mg: iron oxide yellow (E172), iron oxide red (E172) and iron oxide black (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original blister pack or polypropylene container in order to protect from light.

6.5 Nature and contents of container

- PVC/PVdC laminate (clear or white) blister with aluminium foil, inside a carton, containing 7, 10, 14, 20, 28, 30, 50, 98, or 100 tablets.
- Grey polypropylene container of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 Marketing authorisation holder

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

8 Marketing authorisation numbers

4 mg: PA 805/1/1
12 mg: PA 805/1/3
16 mg: PA/805/1/4
20 mg: PA 805/1/5

9 Date of First Authorisation/Renewal of the Authorisation

Date of first authorisation: 13 December 1996

Renewal date: 07 June 2003

10 Date of revision of the text

24/04/07