IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0126/155/004
Case No: 2036128

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Sulpromel 400 mg film Coated Tablet

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **12/06/2007** until **29/02/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sulpromel 400 mg film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of amisulpride.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White round flat tablet with a break line.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Sulpromel is indicated in the treatment of schizophrenia.

4.2 Posology and method of administration

As a general rule, amisulpride is administered once daily at doses up to 400 mg whereas doses above 400 mg are administered twice daily.

Predominant negative episodes
The recommended dosage is from 50 to 300 mg per day. Dosages should be adjusted individually. The optimum dosage is approximately 100 mg per day.

Mixed episodes with positive and negative symptoms.
At the start of treatment the dosage is that which gives optimum control of positive symptoms, that is 400 to 800 mg per day. This dosage is then adjusted individually as a function of the patient's response in order to obtain the minimum effective dose.
Acute psychotic episodes
At the start of treatment,

- Treatment may be started by the IM route for several days at a maximum dose of 400 mg/day and then relayed by the oral route.
- The recommended dosage by the oral route is 400 to 800 mg and the maximum dosage must not exceed 1200 mg.

Subsequently,

- The dosage is maintained or adjusted according to the patient’s response.

In every case the dosage of maintenance therapy will be established individually with the minimum effective dose.

Renal insufficiency:
Because of the renal elimination of amisulpride, the dosage in renal insufficiency should be reduced to half in patients with a creatinine clearance (CR_{CL}) of between 30 and 60 ml/min and to a third in patients with a creatinine clearance of between 10 and 30 ml/min.
As there are no data from patients with severe renal impairment (CR_{CL} <10 ml/min.), amisulpride is contraindicated (see Section 4.3).

Hepatic insufficiency:
As amisulpride is weakly metabolized, a reduction in the dosage should not be necessary in patients with hepatic insufficiency.

4.3 Contraindications

This drug MUST NOT BE USED in the following cases:
- Known hypersensitivity to amisulpride or any other ingredient of the medicinal product.
- Serious hypertensive accidents have been reported in patients with phaeochromocytoma with antidopaminergic drugs including certain benzamides. It is not therefore advisable to prescribe this medicinal product in patients with known or suspected phaeochromocytoma.
- Children under 15 years of age in the absence of any clinical data about this age range.
- Lactation
- Known or suspected prolactin-dependant tumour for example pituitary gland prolactinoma or breast cancer.
- Severe renal insufficiency (CR_{CL} <10 ml/min.).
- In combination with:
    - Sultopride
    - Dopamine agonists except levodopa (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole, selegiline) other than in patients with Parkinson's disease. (see section 4.5).

4.4 Special warnings and precautions for use

Warnings
Neuroleptic Malignant Syndrome
As with other neuroleptics, malignant syndrome (hyperthermia, muscular rigidity, autonomic instability, altered consciousness, elevated CPK) may occur: If the event of hyperthermia, in particular with high daily doses, all anti-psychotic drugs should be discontinued.

Prolonged QT interval
Amisulpride induces a dose-dependent prolongation of the QT interval. This effect, known to potentiate the risk of serious ventricular arrhythmias such as torsades de pointes is enhanced by the pre-existence of bradycardia, hypokalaemia, congenital or acquired long QT interval (combination with a medicinal product increasing the QTc interval).
When the clinical situation permits it is therefore essential before administration to check for the absence of factors that may increase the risk of occurrence of this arrhythmia:
- Bradycardia less than 55 beats per minute,
- Hypokalaemia,
- Congenital prolongation of the QT interval,
- On-going treatment with a medicinal product likely to produce pronounced bradycardia (< 55 beats per minute), hypokalaemia, decreased intracardiac conduction or prolongation of the QTc interval.

It is recommended to record an ECG during the initial examination of patients before they receive long-term neuroleptic therapy.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions for use

Because of the renal elimination of this medicinal product, it is recommended to reduce the dosage in renal insufficiency (see Section 4.2). There are no data in severe renal impairment (see Section 4.3).
Neuroleptics are known to reduce the seizure threshold. Therefore patients with a history of convulsive seizures must be closely monitored during treatment.
Use with caution in elderly subjects because of their high sensitivity (sedation and hypotension)
Caution should also be exercised in Parkinson's disease and neuroleptic treatment must only be used if there is no other alternative.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated
+ Dopamine agonists except levodopa (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole, selegiline) except in Parkinson's disease.
Reciprocal antagonism of effects between dopamine agonists and neuroleptics.
If the neuroleptic induces an extrapyrimidal syndrome do not treat with a dopamine agonist but use an anticholinergic (see section 4.3).

+ Sultopride (benzamide neuroleptic)
Increased risk of ventricular arrhythmia and in particular torsades de pointes (see section 4.3).

Combinations which are not recommended
+ Medications which may induce torsades de pointes: Class Ia antiarrhythmic agents (quinidine, hydroquinidine, disopyramide), class III antiarrhythmic agents (amiodarone, sotalol, dofetilide, ibutilide), certain neuroleptics (thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, tiapride, pimozide, haloperidol, droperidol), others: erythromycin IV, spiramycin IV, halofantrine, pentamidine, sparfloxacin, moxifloxacin, gatifloxacin, bepridil, cisapride, diphemanil, mizolastine, vincamine IV.
Increased risk of ventricular arrhythmia and in particular torsades de pointes.
If possible discontinue the non anti-infective torsade-inducing agent. If combination cannot be avoided, first control the QT interval and continuously monitor the ECG (see section 4.4).

+ Alcohol
Potentiation by alcohol of the sedative effect of neuroleptics.
The reduction in vigilance may make it difficult to drive a vehicle or operate machinery.
Avoid the consumption of alcoholic beverages or drugs containing alcohol.

+ Levodopa
Reciprocal antagonism of effects between levodopa and neuroleptics. In Parkinson's disease patients, use the minimum effective doses of each of the two drugs.

+ Dopamine agonists except levodopa (amantadine, apomorphine, bromocriptine, cabergoline, entacapone, lisuride, pergolide, piribedil, pramipexole, quinagolide, ropinirole, selegiline) in Parkinson's disease patients.
Reciprocal antagonism of effects between dopamine agonist and neuroleptics. The dopamine agonist may induce or worsen pre-existing psychotic disorders. If neuroleptic treatment is essential in Parkinson's disease patients receiving dopamine agonists, the latter drugs must be gradually tapered until complete discontinuation (sudden interruption of dopaminergics increases the risk of neuroleptic malignant syndrome).

Combinations which require precautions for use
+ Bradycardia-inducing medications (bradycardia-inducing calcium channel blockers: diltiazem, verapamil; beta blockers except sotalol (see Combinations which are not recommended); clonidine; guanfacine; mefloquine; digitalis glycosides, anticholinesterases: donepezil, rivastigmine, tacrine, ambenonium, galantamine, pyridostigmine, neostigmine)

Increased risk of ventricular arrhythmias and in particular torsades de pointes. Clinical and electrocardiographic

monitoring.

+ Medications which induce hypokaemia (hypokalemic diuretics, stimulant laxatives, amphotericin B (IV route), glucocorticoids, tetracosactide)
Increased risk of ventricular arrhythmias and in particular torsades de pointes. Correct any hypokalaemia before administration of the product and maintain clinical, electrolyte and electrocardiographic monitoring.

Combinations to be taken into account:
+ Antihypertensive agents (all):
Potentiation of antihypertensive effect and risk of orthostatic hypotension (additive effect).

+ Other CNS depressants:
Morphine derivatives (analgesics, anti-tussives and substitution treatments); barbiturates; benzodiazepines; anxiolytics other than benzodiazepines; hypnotics; neuroleptics; sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine); sedative H1 antihistamines; centrally acting antihypertensives; others: baclofen, thalidomide, pizotifen.
Potentiation of central depression. The reduction in vigilance may make it difficult to drive a vehicle or operate machinery.

+ Betablockers in heart failure (bisoprolol, carvedilol, metoprolol): Vasodilator effects and risk of hypotension, and in particular orthostatic hypotension (additive effect).

4.6 Pregnancy and lactation

Pregnancy
No teratogenic effect has been observed in studies on experimental animals: Amisulpride is not expected to cause malformations in humans as it is not teratogenic in experimental animals. To date, all substances responsible for malformations in humans have been shown to be teratogenic in animals during well-conducted studies on two animal species.
There are currently insufficient clinical data to evaluate any malformative or foetotoxic effect of amisulpride when it is administered during pregnancy.
Consequently, as a precaution, amisulpride should not be used during pregnancy.

Lactation
As it is not known whether amisulpride is excreted in breast milk, breast-feeding is contra-indicated.

4.7 Effects on ability to drive and use machines

Patients are warned that this drug may cause drowsiness and have an influence on the ability to drive and use machines.

4.8 Undesirable effects

Disorders of the central nervous system
Common:
- Insomnia, anxiety, agitation,
- Extrapyramidal symptoms may occur (tremors, hypertonia, hypersalivation, akathisia, hypokinesia). These symptoms are generally mild at maintenance dosages and partially reversible without discontinuation of Sulpromel, upon administration of anticholinergic antiparkinsonian medication.
  The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.
  In studies, patients treated with amisulpride presented a lower incidence of extrapyramidal symptoms than patients treated with haloperidol.

Less common:

- Daytime drowsiness.

Very rarely:
- Acute dystonia (spasmodic torticollis, oculogyric crises, trismus) may occur, This is reversible without discontinuation of treatment upon administration of an anticholinergic antiparkinsonian agent.
- Tardive dyskinesia characterised by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration.
  Anticholinergic antiparkinsonian medication is ineffective or may induce aggravation.
- Cases of convulsive seizures.
- Cases of malignant syndrome (cf. 4.4 Special warnings and special precautions for use)

Endocrine and metabolic disorders
Common:
- Increased prolactin levels which are reversible on discontinuation of treatment which may lead to the following clinical signs: galactorrhoea, amenorrhoea, gynaecomastia, breast pain, impotence and orgasmic dysfunction.
- Weight gain.

Gastrointestinal disorders:
Less common:
- Constipation, nausea, vomiting and dryness of the mouth.

Cardiac disorders
Very rarely:
- Cases of hypotension and bradycardia.
- Cases of prolonged QT interval and very rare cases of torsades de pointes have been reported (cf. Special warning).

Hepatic disorders
Very rarely:
- Elevations of hepatic enzymes and mainly transaminases have been reported.

Systemic disorders
Very rarely:
- allergic reactions

4.9 Overdose

Experience with amisulpride in acute overdosage is limited. The reported signs and symptoms were those generally due to an exaggeration of the known pharmacological effects of the medicinal product leading clinically to: drowsiness, sedation, coma, hypotension and extrapyramidal symptoms.
There is no known specific antidote to amisulpride. In the case of acute overdosage, combination with other drugs must be looked for and the appropriate measures must be taken:
- Close supervision of vital functions.
- Continuous cardiac monitoring (risk of prolongation of QT interval) which must be continued until the patient has recovered.
- If severe extrapyramidal symptoms occur, anticholinergic treatment must be instituted.
- Since amisulpride is only weakly dialyzable, haemodialysis is only of limited value to eliminate this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIPSYCHOTICS, ATC Code: N05AL05.
(N: Central Nervous System)

Amisulpride is an anti-psychotic in the substituted benzamide class.
Its pharmacodynamic profile is characterized by a selective and predominant affinity for D2 and D3 dopaminergic receptors of the limbic system. Amisulpride is devoid of affinity for serotoninergic receptors or for other histamine, cholinergic and adrenergic neuroreceptors.
At high doses in studies conducted in experimental animals, amisulpride preferentially blocked the dopaminergic neurons located in the limbic structures in preference with those of the striatum. This specific activity may be explained by the fact that the antipsychotic effects of amisulpride predominate over the extrapyramidal effects.
At low doses, amisulpride preferentially blocks the presynaptic D2/D3 dopaminergic receptors which may explain its action on the negative symptoms.
In a controlled double-blind trial versus haloperidol including 191 patients with acute schizophrenia, amisulpride was associated with a significantly greater improvement in the negative symptoms than the comparator.

5.2 Pharmacokinetic properties

Amisulpride has two absorption peaks in humans: a first peak which is rapidly reached one hour after the dose and a second reached three or four hours after administration.
The corresponding plasma levels were 39 ± 3 and 54 ± 4 ng/ml respectively after administration of a 50-mg dose.
The volume of distribution is 5.8 l/kg. Plasma protein binding is low (16 %) and does not suggest the occurrence of drug interactions at the level of plasma protein binding. The absolute bioavailability is 48%.
Amisulpride is only slightly metabolized: two inactive metabolites have been identified and represent 4% of the total quantity eliminated.
There was no accumulation of amisulpride or any change in the pharmacokinetic
parameters after repeated administration of amisulpride.
The elimination half-life is approximately 12 hours after an oral dose.
Amisulpride is eliminated in unchanged form in the urine; 50% of the dose administered by the IV route is eliminated in the urine, mainly during the first 24 hours (90% of urinary excretion).
The renal clearance is approximately 330 ml/min. A high-carbohydrate meal significantly reduces the AUC, Tmax and Cmax of amisulpride whereas a high-fat meal does not modify these parameters; the effect of these results on amisulpride treatment is unknown.

Hepatic insufficiency
As amisulpride is weakly metabolized a reduction in the dosage should not be necessary in patients with hepatic insufficiency.

Renal insufficiency
The elimination half-life is unchanged in patients with impaired renal function whereas the total clearance is reduced by a factor of from 2.5 to 3.
The AUC of amisulpride is multiplied by 2 in patients with mild renal insufficiency by nearly 10 in cases of moderate renal insufficiency.
Experience however is limited and there are no available data for doses greater than 50 mg.
Amisulpride is very weakly dialyzed.

Elderly subjects
Available pharmacokinetic data in elderly subjects aged over 65 years show an increase of 10 to 30% in Cmax, T 1/2 and AUC after a single 50-mg dose.
There are no available data after repeated doses.

5.3 Preclinical safety data

The toxicological profile of amisulpride is dominated by the pharmacological effects of the molecule. No target organ was revealed by the repeat-dose toxicity studies. The molecule is devoid of any teratogenic or genotoxic risk. Carcinogenicity studies demonstrated hormone-dependant tumours in rodents. These have no clinical pertinence in humans.
A reduction in the fertility related to the pharmacological properties of the product (prolactin-mediated effects) was observed in experimental animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Sodium Starch Glycolate (Type A)
Microcrystalline cellulose
Methylcellulose
Magnesium stearate.

Film-coating:
Basic butylated methacrylate copolymer
Talc
Titanium dioxide (E171)
Magnesium stearate
Macrogol 6000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

There are no special precautions for storage.

6.5 Nature and contents of container

30, 60 or 150 tablets in thermoformed blister packs (PVC/aluminium).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd.
Waterford Road
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 126/155/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date for authorisation: 2nd March 2007

10 DATE OF REVISION OF THE TEXT

June 2007