IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0013/082/001
Case No: 2020829

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

Novartis Pharmaceuticals UK Ltd

Frimley Business Park,, **Frimley,**, **Surrey, GU16 7SR**, **England**

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

SYMMETREL 100 mg Capsule

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 **09/05/2006** .

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

Symmetrel 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg Amantadine Hydrochloride

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Capsule, Hard
Brownish-red, flexible gelatin capsule, imprinted 'GEIGY'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of Parkinson's disease.
Herpes zoster.

Prophylactic treatment against influenza type A illness.

4.2 Posology and method of adminstration

Adults:

Parkinson's disease:

The optimum dosage may differ from patient to patient.
100 mg Symmetrel daily can be added to existing therapy. Depending on clinical response, this dosage may, after one week, be increased to 100 mg twice daily.

Herpes zoster:

The treatment should be started as soon as possible after the diagnosis has been made. The dosage is 100mg twice daily for 14 days. If post-herpetic pain persists after this period it is recommended that treatment be continued for a further 14 days.

Prophylactic treatment against Type A virus influenza:

Children aged 5-9 years: 1 capsule once daily.
Children and adults aged 10-65 years: 1 capsule twice daily. Effective prevention and treatment of influenza A have been reported with a dosage of 100 mg daily. This dosage may be indicated for persons who have demonstrated intolerance to 200mg Symmetrel daily.

Adults aged over 65 years: plasma amantadine concentrations are influenced by renal function. In the elderly the elimination half-life tends to be longer and renal clearance lower than in younger subjects. A dose not exceeded 100 mg daily is therefore recommended in elderly patients without renal disease. If the patient has any renal function impairment, the dose should be further reduced.

Prevention: For prophylaxis this regimen should be started in anticipation of contact and continued for the duration of the influenza A outbreak, usually for approximately 6 weeks. When used with inactivated influenza A vaccine, amantadine is continued for 2 to 3 weeks after administration of the vaccine.

Treatment: it is advisable to start treating influenza as early as possible and continue for 4 to 5 days. When amantadine is started within 48 hours of symptoms appearing, the duration of fever and other effects is reduced by 1 or 2 days and the inflammatory reaction of the minor bronchial tree that usually accompanies influenza resolves more quickly.

4.3 Contraindications

Known hypersensitivity to amantadine, rimantadine or to any agent in the adamantane class.

Amantadine is also contraindicated in bipolar patients, in whom it can trigger mania. Use is contraindicated in individuals who are subject to convulsions, or who have existent gastric ulceration.

4.4 Special warnings and precautions for use

Patients with pre-existing seizure disorders have been reported to develop an increased frequency of major motor seizures during amantadine therapy. A reduction in dosage may minimise this risk. These patients should be closely monitored.
An increase in hallucinations, confusion, and nightmares may occur in patients with underlying psychiatric disorders.

Owing to the possibility of serious adverse effects, caution should be observed when prescribing Symmetrel to patients being treated with drugs that have central nervous system (CNS) effects, or for whom the potential risks outweigh the benefits of treatment. Because some patients have attempted suicide on amantadine, prescriptions should be written for the smallest quantity consistent with good patient management.

Peripheral oedema, probably due to local vascular disturbance, may occur during treatment with Symmetrel. This should be taken into account in patients with a history of heart failure.

Particular care is called for in patients suffering from, or with a history of, recurrent eczema, gastric ulceration, or cardiovascular disorders.

Symmetrel should be used cautiously in patients with liver or renal disorders. In cases of impaired renal function, the dosage should be adjusted according to the creatinine clearance of the individual patient and, ideally, plasma amantadine concentrations should be monitored. Since only small amounts of amantadine are eliminated by patients undergoing haemodialysis for renal failure, these patients should have their dosage carefully adjusted in order to avoid adverse reactions.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take thise medicine.

Discontinuation of treatment
Abrupt discontinuation of amantadine may result in worsening of the symptoms of Parkinson’s disease e.g. increased rigidity, confusion, urinary retention or bulbar palsy. There have been isolated reports on a possible association between the occurrence of neuroleptic malignant syndrome(NMS)-like symptoms and abrupt cessation of amantadine; furthermore, there have been isolated reports on a possible association between the aggravation of NMS or neuroleptic-induced catatonia and the withdrawal of amantadine in patients concurrently taking neuroleptic agents. Treatment with amantadine should therefore not be stopped abruptly.

4.5 Interaction with other medicinal products and other forms of interaction

Ethanol should not be used with amantadine because of the possible increase of CNS effects such as dizziness, confusion, lightheadedness, fainting, or orthostatic hypotension.

Amantadine should be used with caution with anticholinergics, tricyclic antidepressants, antihistamines, or phenothiazines because of the possible increase of anticholinergic effects, especially hallucinations, nightmares, or confusion. Reductions in the dosage of both drugs may be necessary before using them together.

Amantadine can produce undesirable reactions if opiate agonists are used concomitantly in large doses. Usual therapeutic doses should not produce any interaction.

Amantadine can increase the efficiency of levodopa by its action on central nerve terminals. Patients who exhibit psychoses should avoid this combination because of the possibility of an increased psychotic effect.

Amantadine used concomitantly with CNS stimulants can result in increased stimulant effects, such as nervousness, irritability, or insomnia, and can lead to seizures or cardiac arrhythmias. Close monitoring of the patient is recommended.

Mental status changes have been reported after co-trimoxazole was administered to a patient taking amantadine. Although it is not clear which drug in co-trimoxazole may be responsible, trimethoprim and amantadine both undergo tubular secretion. As a result, each drug can interfere with the renal clearance of the other. Trimethoprim should be used cautiously in patients receiving therapy with amantadine.

There have been isolated reports of a suspected interaction between amantadine and combination diuretics (hydrochlorothiazide and potassium-sparing diuretics e.g. triamterene). One or both of the components apparently reduce the clearance of amantadine, leading to higher plasma concentrations and toxic effects (confusion, hallucinations, ataxia, myoclonus).

4.6 Pregnancy and lactation

The drug should not be administered during pregnancy unless considered essential by the physician. The drug is excreted in breast milk. Studies in animals have shown that amantadine at high doses is embryotoxic in rats but not in rabbits. No evidence is available concerning such an effect in human beings.

4.7 Effects on ability to drive and use machines

Symmetrel may impair a patient’s reactions. Due caution is required when driving or operating machinery.

4.8 Undesirable effects

The undesirable effects of amantadine are often of a mild and transient nature. They usually appear within the first 2-4 days of treatment and promptly disappear within 24-48 hours of discontinuation of amantadine.

A direct relationship between dose and incidence of side effects has not been demonstrated; however, there seems to be a tendency towards more frequent undesirable effects (particularly affecting the central nervous system) with increasing doses.

Central nervous system

Occasional: depression, anxiety, elevation of mood, agitation, nervousness, difficulty in concentrating, dizziness, lightheadedness, headache, insomnia, lethargy, hallucination, nightmares, ataxia, slurred speech, blurred vision.

Hallucinations, confusion and nightmares are more common when amantadine is administered concurrently with anticholinergic agents or when the patient has an underlying psychiatric disorder.

Rare: confusion, disorientation, psychosis, tremor, dyskinesia, convulsions.

Isolated cases: NMS-like symptoms.

Delirium, hypomanic state, and mania have been reported but their incidence cannot be readily deduced from the literature.

Cardiovascular system

Frequent: oedema of ankles, livedo reticularis.

Occasional: palpitations, orthostatic hypotension.

Isolated cases: heart insufficiency/failure.

Blood

Isolated cases: leukopenia, reversible elevation of liver enzymes.

Gastrointestinal system

Occasional: dry mouth, anorexia, nausea, vomiting, constipation.

Rare: diarrhoea.

Skin and appendages

Occasional: diaphoresis

Rare: exanthema.

Isolated cases: photosensitisation.

Sense organs

Rare: corneal lesion, e.g. punctate subepithelial opacities which might be associated with superficial punctate keratitis, corneal epithelial oedema, and markedly reduced visual acuity.

Urogenital system

Rare: urinary retention, urinary incontinence.

4.9 Overdose

Signs and symptoms

Neuromuscular disturbances and symptoms of acute psychosis are prominent features of acute poisoning with amantadine.

Central nervous system

Hyperreflexia, motor restlessness; convulsions; extrapyramidal signs; torsion spasms, dystonic posturing; dilated pupils. Confusion, disorientation, delirium, visual hallucinations.

Respiratory system

Hyperventilation, pulmonary oedema, respiratory distress, including adult respiratory distress syndrome.

Cardiovascular system

Sinus tachycardia, arrhythmia.

Gastrointestinal system

Nausea, vomiting, dry mouth.

Renal function

Urinary retention, renal dysfunction, including increase in BUN and decreased creatinine clearance.

Overdose from combined drug treatment

The peripheral and central adverse effects of anticholinergic drugs are increased by the concomitant use of amantadine, and acute psychotic reactions, which may be identical to those caused by atropine poisoning, may occur when large doses of anticholinergic agents are used. Where alcohol or central nervous stimulants have been taken at the same time, the signs and symptoms of acute poisoning with amantadine may be aggravated and/or modified.

Management

There is no specific antidote.

Removal and/or inactivation of poisoning agent(s): induction of vomiting and/or gastric aspiration and lavage if patient is conscious, activated charcoal, saline cathartic, if judged appropriate. Since amantadine is largely excreted unchanged in the urine, maintenance of renal excretory function, copious diuresis, and forced diuresis, if necessary, are effective in removing it from the blood stream. Acidification of the urine favours the excretion of amantadine in the urine. Haemodialysis does not remove significant amounts of Symmetrel; in patients with renal failure, four-hour haemodialysis removed 7 to 15 mg after a single 300 mg oral dose.

Monitoring of blood pressure, heart rate, ECG, respiration, body temperature, and treatment for possible hypotension and cardiac arrhythmias, as necessary.

Convulsions and excessive motor restlessness: administer anticonvulsants such as diazepam i.v., paraldehyde i.m. or per rectum, or phenobarbital i.m.

Acute psychotic symptoms, delirium, dystonic posturing, myoclonic manifestations: physostigmine by slow i.v. infusion (1 mg doses in adults, 0.5 mg in children) in repeated administration according to initial response and subsequent need has been reported.

Retention of urine: The bladder should be catheterised; an indwelling catheter can be left in place for the time required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mode of action:
Amantadine increases dopaminergic activity by enhancing the release of Dopamine from central neurones and delaying the re-uptake into synaptic vesicles.

5.2 Pharmacokinetic properties

Amantadine is absorbed slowly but almost completely. Peak plasma levels of 250 ng/ml are achieved within approximately 3 to 4 hours after a single oral administration of 100 mg.

It is extensively bound to tissue and plasma proteins and has an apparent volume of distribution of 5 to 10 L/Kg. Amantadine accumulates in the nasal secretions after several hours and also crosses the blood brain barrier but in non-quantifiable levels.

It is excreted mainly unchanged in urine with a mean plasma half-life of about 15 hours, prolonged in the elderly.

5.3 Preclinical safety data

Amantadine hydrochloride has a low degree of acute toxicity in several animal species.

Subchronic oral toxicity studies were conducted in rats, dogs and monkeys at dosages up to 160, 30 and 100 mg/Kg, respectively. There was no evidence of specific toxicity.

Chronic oral toxicity studies with two years treatment of rats and dogs at doses of up to 160 and 80 mg/Kg respectively did not reveal specific toxicity.

Reproduction toxicity studies :
Symmetrel has been reported to be embryotoxic and teratogenic in rats at 50mg/kg/day, which is about 12 times the recommended human dose, but not at 37 mg/kg/day.

Embryotoxic and teratogenic effects were not seen in rabbits which received up to 25 times the usual recommended adult human dose.
In rats oral doses of 50 and 100 mg/Kg proved to be teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Povidone (E1201)
Magnesium Stearate
Red Iron Oxide (E172)
Titanium Dioxide (E171)
Gelatin

Printing Ink

(Opacode White) containing colouring Titanium Dioxide (E171)

Shellac (E904)
Soya Lecithin MC Thin
Antifoam DC 1510

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Securitainers: Keep container tightly closed.
Blisters: Store in the original package.

6.5 Nature and contents of container

Securitainers of 100 capsules.
PVC/PVdC blister strips of 4 x 14 (56) capsules.

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

Novartis Pharmaceuticals UK Limited
Frimley Business Park
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Camberley
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England

8 MARKETING AUTHORISATION NUMBER

PA 13/82/01

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd November 1976

Date of last renewal: 1st December 2005

10 DATE OF REVISION OF THE TEXT

February 2006