NOVARTIS

Drug Regulatory Affairs

SYMMETREL®

(amantadine)

100 mg soft capsules

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

SYMMETREL® 100 mg soft capsules

2 Qualitative and quantitative composition

Active ingredient: 1-Adamantanamine hydrochloride (= amantadine hydrochloride): 100 mg.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Soft capsules.

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Treatment of Parkinson's disease

- Idiopathic parkinsonism,
- Secondary parkinsonism (e.g. of post-encephalitic type, of cerebrovascular origin or drug-induced parkinsonism) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Symmetrel can be given alone for initial therapy or combined with anticholinergic drugs or L-dopa.

Prevention and treatment of signs and symptoms of infection caused by various strains of influenza A virus

For individual and mass prophylaxis in subjects exposed to risk of infection, particularly when vaccination is unavailable or contraindicated; post-exposure prophylaxis in conjunction with inactivated vaccine during an outbreak until protective antibodies develop or in patients who are not expected to have a substantial antibody response (immunosuppression); control of institutional outbreaks. Because Symmetrel does not completely prevent the host immune response to influenza A infection, individuals who take this drug may still develop immune responses to natural disease or vaccination and may be protected when later exposed to antigenically related viruses.

Amantadine is effective in the treatment of active influenza A infection when administered within 48 hours after the onset of symptoms.

When using Symmetrel, either in individuals or in groups of patients, it is essential that the treatment be given under medical supervision.

Some evidence for relief of pain in acute herpes zoster has been reported.

4.2 Posology and method of administration

Parkinson's disease

Initially 1 capsule daily, increased after one week to 1 capsule twice daily. The dose can be titrated against signs and symptoms. Amounts exceeding 200 mg daily may provide some additional relief but may also be associated with increasing toxicity. In these cases the dose should be raised gradually, at intervals of not less than 1-week. Amantadine acts within a few days but often appears to lose some of its efficacy within a few months of continuous treatment.

The effectiveness of amantadine may be prolonged by a temporary withdrawal, which seems to restore activity.

Treatment with Symmetrel must be reduced gradually, because abrupt discontinuation may exacerbate Parkinson's syndrome, regardless of the patient's response to therapy (see section 4.4 Special warnings and precautions for use).

Combined treatment: Any antiparkinsonian drug with which the patient is already being treated should be continued during the first stage of treatment with Symmetrel. In many cases it is then possible gradually to reduce the dosage of the other drug without prejudicing the treatment response. If increased side effects occur, however, its dosage should be reduced more quickly. In patients already receiving large doses of anticholinergic agents or L-dopa the initial low-dosage phase of treatment with Symmetrel should be extended to 15 days.

Type A virus influenza - prevention and treatment

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 200 mg Symmetrel daily.

Adults aged over 65 years: see section 4.2 Posology and method of administration - Use in elderly patients.

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.

Use in elderly patients

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 exceeding 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.

Dosage in renal impairment

In patients with compromised renal function and under haemodialysis the elimination half-life of amantadine is substantially prolonged, resulting in elevated plasma concentrations. Careful adjustment of the dose of Symmetrel by increasing the dosing interval according creatinine clearance (see table) is required in these patients, following a loading dose on first day of 200 mg.

Creatinine clearance [mL/(min 1.73 m^2)]	100 mg dose interval
< 15	7 days
15-25	3 days
25-35	2 days
35-75	1 day
> 75	12 hours

Ideally, plasma amantadine concentrations should be monitored. Careful surveillance of the patient is recommended (see section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Pregnancy.

Known hypersensitivity to amantadine or to any of the excipients of Symmetrel.

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 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 (see section 4.2 Posology and method of administration).

Hypothermia has been observed in children, especially in those younger than 5 years of age. Caution should be exercised when prescribing Symmetrel to children for the prevention and treatment of influenza type A virus (see also section 4.2 Posology and method of administration).

Because amantadine has anticholinergic effects, it should not be given to patients with untreated angle closure glaucoma.

Discontinuation of treatment

Abrupt discontinuation of amantadine may result in worsening of the symptoms of Parkinson's disease or in symptoms resembling neuroleptic malignant syndrome (NMS), as well as in cognitive manifestations (e.g. catatonia, confusion, disorientation, worsening of mental status, delirium). 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.

Resistance

Resistance to amantadine and rimantadine is readily achieved by serial passage of influenza virus strains *in vitro* or *in vivo* in the presence of the drug. Influenza A viruses (cross-)resistant to amantadine and rimantadine can emerge when these drugs are used to treat influenza infections. Apparent transmission of drug-resistant viruses may have been the reason for failure of prophylaxis and treatment in household contacts and nursing-home patients. However, there is no evidence to date that the resistant virus produces a disease that is in any way different from that produced by sensitive viruses.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of amantadine and anticholinergic agents or levodopa may increase confusion, hallucinations, nightmares, gastrointestinal disturbances, or other atropine-like side effects (see section 4.9 Overdose).

In isolated cases psychotic decompensation has been reported in patients receiving amantadine and concomitant neuroleptic medication or levodopa.

Concurrent administration of amantadine and drugs or substances (e.g. alcohol) acting on the central nervous system may result in additive CNS toxicity. Close observation is recommended (see section 4.9 Overdose).

There have been isolated reports of a suspected interaction between amantadine and combination diuretics (hydrochlorothiazide + potassium-sparing diuretics). 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

Pregnancy

Reproductive toxicity studies were performed in rats and rabbits. In rats oral doses of 50 and 100 mg/kg proved to be teratogenic.

Amantadine-related complications during pregnancy have been reported. Symmetrel is contraindicated during pregnancy and in women wishing to become pregnant.

Lactation

Amantadine passes into breast milk. Undesirable effects have been reported in breast-fed infants. Nursing mothers should not take Symmetrel.

4.7 Effects on ability to drive and use machines

Patients receiving Symmetrel should be warned that dizziness, blurred vision and other central nervous symptoms (see section 4.8 Undesirable effects) may occur and impair the reaction of the patient, in which case they should not drive or use machines.

4.8 Undesirable effects

Amantadine's undesirable effects 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, hallucinations, 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 tract

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

Rare: diarrhoea.

Skin and appendages

Occasional: diaphoresis.

Rare: exanthema.

Isolated cases: photosensitization.

Sense organs

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

Urogenital tract

Rare: urinary retention, urinary incontinence.

General disorders

In post-marketing exposure hypothermia has been reported in children mainly those younger than 5 years of age (see also section 4.4 Special warnings and precautions for use). The frequency can not be established.

4.9 Overdose

Overdose with Symmetrel can lead to fatal outcome.

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, dysphagia. Confusion, disorientation, delirium, visual hallucinations, myoclonus.

Respiratory system

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

Cardiovascular system

Cardiac arrest and sudden cardiac death have been reported. Sinus tachycardia, arrhythmia, hypertension.

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 catheterized; an indwelling catheter can be left in place for the time required.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiparkinsonian agent and anti-influenzal virostatic (ATC code N04B B01).

As antiparkinsonian agent

Amantadine is believed to act by enhancing the release of dopamine from central neurons and by delaying its reuptake into synaptic vesicles.

It may also exert some anticholinergic activity.

When administered either alone or in combination with other drugs, amantadine produces an improvement in the cardinal signs and symptoms of parkinsonism and improves functional capacity.

The effect generally sets in two to five days after the start of treatment. It exerts a positive effect, particularly on akinesia, rigidity, and tremor.

As anti-influenzal virostatic

Amantadine specifically inhibits the replication of influenza A viruses at low concentrations. Using a sensitive plaque-reduction assay human influenza A viruses including H_1N_1, H_2N_2, H_3N_2 subtypes, are inhibited by 0.4 µg/mL or less of amantadine.

The exact mechanism of action of amantadine is unclear, but it appears to inhibit an early stage in viral replication, possibly uncoating the viral genome in lysosomes. Effects on late replicative steps with impaired assembly of virus has been found for certain avian influenza viruses.

5.2 Pharmacokinetic properties

Absorption

Amantadine is absorbed slowly but almost completely. Peak plasma concentrations of approximately 250 ng/mL and 500 ng/mL are attained within 3-4 hours after single oral administration of 100 mg and 200 mg amantadine, respectively.

Following repeated administration of 200 mg daily the steady-state plasma concentration settles at 300 ng/mL within 3 days.

Distribution

In vitro, 67% of amantadine is bound to plasma proteins. A substantial amount of amantadine is bound to red blood cells. The erythrocyte amantadine concentration in normal healthy volunteers is 2.66 times the plasma concentration.

The apparent volume of distribution ($V_{D)}$ of the drug is 5-10 L/kg, suggesting extensive tissue binding. It declines with increasing doses. The concentration of amantadine in the lung, heart, kidney, liver, and spleen is higher than in the blood.

The drug accumulates in nasal secretions after several hours.

Amantadine crosses the blood-brain barrier; however, it is not possible to quantify this event.

Biotransformation

Amantadine is metabolized to a minor extent, principally by N-acetylation. Whether this metabolic pathway is affected by acetylator phenotype remains to be determined.

Elimination

The drug is eliminated in healthy young adults with a mean plasma elimination half-life of 15 hours (10-31 hours).

Total plasma clearance is about the same as renal clearance (250 mL/min). Renal amantadine clearance is much higher than the creatinine clearance, suggesting renal tubular secretion.

A single dose of amantadine is excreted over 72 hours as follows: 65-85% unchanged, 5-15% as acetyl metabolite in urine, and 1% in faeces. After 4-5 days 90% of the dose appears unchanged in urine. The rate is considerably influenced by urinary pH. A rise in pH brings about a fall in excretion.

Characteristics in patients

Elderly patients

Compared with data from healthy young adults, the t1/2 is doubled, and renal clearance is diminished. The renal/creatinine clearance ratio in elderly subjects is smaller than in young people. Tubular secretion diminishes more than glomerular filtration in the elderly. In elderly patients with renal function impairment repeated administration of 100 mg daily for 14 days raised the plasma concentration into the toxic range.

Renal failure

Accumulation of amantadine may occur in renal failure causing severe adverse drug reactions. A creatinine clearance of less than 40 mL/[min. 1.73 m^2] causes a 3- to 5-fold increase in t1/2 and a 5-fold decrease in total and renal clearance. Renal elimination is dominant even in cases of renal failure.

Elderly patients or patients suffering from renal failure should receive an adequately reduced dosage in accordance with individual creatinine clearance. The target plasma amantadine concentration should not exceed a maximum of 300 ng/mL.

Haemodialysis

Little amantadine is removed by haemodialysis; this inefficiency may be related to its extensive tissue binding. Less than 5% of a dose is eliminated after 4-hour haemodialysis. The mean t1/2 reaches 24 dialysis -hours.

5.3 Preclinical safety data

Amantadine hydrochloride exhibited a low degree of acute toxicity in several animal species. Subchronic oral toxicity studies were carried out in rats, dogs and monkeys at a

dosage up to 160, 30, and 100 mg/kg, respectively. There was no evidence of specific toxicity. Chronic toxicity studies with administration to rats and dogs over a period of up to two years of oral doses up to 160 and 80 mg/kg, respectively, did not disclose specific toxicity.

Moreover, there was no clear evidence of a carcinogenic potential. In view of the experimental design of these studies, the latter statement, however, is of doubtful significance.

A single chromosomal aberration test showed a marginal increase in the incidence of chromosome breaks. In the absence of further relevant mutagenicity studies, no conclusive evidence can be furnished with regard to the question of mutagenic potential.

6 Pharmaceutical particulars

6.1 List of excipients

Rapeseed oil; soybean lecithin; wax blend composed of one part beeswax, one part hydrogenated soybean oil, four parts other partially hydrogenated vegetable oils.

Information might differ in some countries.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

Information might differ in some countries.

6.4 Special precautions for storage

Protect from moisture and heat (do not store above 30°C).

Symmetrel should be kept out of the reach and sight of children.

Information might differ in some countries.

6.5 Nature and contents of container

Country specific.