NOVARTIS

SYMMETREL 100®

(Amantadine hydrochloride)

100 mg, Soft Capsules

Professional Information

Document status: Final

Release date: 30 October 2024

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Confidential

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Scheduling status: **S4**

Proprietary name (and dosage form)

SYMMETREL 100® Soft Capsules

Composition

Each capsule contains 1-Adamantanamine hydrochloride (= amantadine hydrochloride) 100 mg

Pharmacological classification

A 20.2.8 Antiviral agents

Pharmacological action

Amantadine is believed to act by enhancing the release of dopamine from neurons and by delaying its re-uptake into synaptic vesicles. It may also exert some anticholinergic activity.

Amantadine exerts an effect, on akinesia, rigidity and tremor in Parkinson's disease.

Amantadine inhibits the replication of influenza A viruses.

Pharmacokinetics

Absorption

Amantadine is absorbed slowly but almost completely. Peak plasma concentrations are attained within 2 to 4 hours after single oral administration of amantadine. Following repeated administration of 200 mg daily, the steady-state plasma concentration settles at 300 ng/mL within 3 days.

Distribution

In vitro, 67 % is bound to plasma proteins. 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 large, suggesting extensive tissue binding. The drug accumulates after several hours in nasal secretions. Amantadine crosses the blood-brain barrier.

Biotransformation

Amantadine is metabolised to a minor extent, principally by N-acetylation.

Elimination

In healthy young adults, amantadine is eliminated with a mean plasma elimination half-life of 15 hours (10 to 31 hours). Total plasma clearance is about the same as renal clearance (250 mL/minute). 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 to 85 % unchanged, 5 to 15 % as acetyl metabolite in urine and 1 % in faeces. 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.

Elderly patients

In elderly patients the half-life is doubled and renal clearance is diminished. The renal/creatinine clearance ratio in elderly subjects is smaller than in young people. Tubular secretion appears to diminish more than glomerular filtration in the elderly. Repeated administration of 100 mg daily in elderly patients may raise the plasma concentration to toxic range.

Renal failure

In patients with impaired renal function accumulation of amantadine may occur causing severe adverse drug reactions. A creatinine clearance of less than 40 mL/(min. x 1,73 m^2) causes an increase in half-life and a 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

In haemodialysis, less than 5 % of a dose is eliminated after 4 hours. The mean half-life reaches 24 dialysis-hours.

Indications

Parkinson's syndrome

Parkinson's disease (paralysis agitans); Symptomatic Parkinsonism (of post-encephalitic types or of cerebrovascular origin).

A Virus Influenza

For individual and mass prophylaxis in subjects exposed to the risk of infection.

Individuals, who take SYMMETREL, may still develop immune response to natural infections or vaccination and may be protected when later exposed to antigenically related viruses, because SYMMETREL does not completely prevent the host immune response to influenza A infection.

For treatment in the early stages of infection (1st to 2nd day of illness). When employing SYMMETREL, either in individuals or in groups of patients, it is essential that the treatment be given under medical supervision.

Contra-indications

Known hypersensitivity to amantadine or to any of the excipients of SYMMETREL. Pregnancy and lactation. *(See Pregnancy and Lactation).*

*C*onfusional, hallucinatory or epileptiform states.

Severe renal or hepatic disease.

Warnings

Patients with pre-existing seizure disorders have been reported to develop an increased frequency of major motor seizures during SYMMETREL 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 agents that have central nervous system effects, or for whom the potential risks outweigh the benefits of treatment. Because

some patients have attempted suicide on SYMMETREL, prescriptions should be written for the smallest quantity consistent with good patient management.

SYMMETREL should not be used by children under 5 years of age.

Discontinuation of treatment

Abrupt discontinuation of SYMMETREL may result in a 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 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 SYMMETREL should therefore not be stopped abruptly.

Resistance

Resistance to amantadine 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 SYMMETREL and rimantadine can emerge when these agents are used to treat influenza infections.

Interactions

Concurrent administration of SYMMETREL and anticholinergic agents or levodopa may increase confusion, hallucinations, nightmares, gastro-intestinal disturbances, or other atropine-like side-effects.

Psychotic decompensation has been reported in patients receiving SYMMETREL and concomitant neuroleptic medication or levodopa.

Concurrent administration of SYMMETREL and agents or substances (e.g. alcohol) acting on the central nervous system may result in additive central nervous system toxicity. Close observation is recommended.

There have been isolated reports of a suspected interaction between SYMMETREL 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).

No stimulant agents, e.g. sympathomimetics or appetite-depressants should be administered to patients receiving SYMMETREL.

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. Adequate measures to prevent pregnancy should therefore be taken *(See Contraindications).*

Lactation

SYMMETREL passes into breastmilk. Undesirable effects have been reported in breastfed infants. Breastfeeding mothers should not take SYMMETREL.

Dosage and directions for use

SYMMETREL should be taken at mealtimes, preferably in the morning and at midday.

Parkinson's syndrome

Irrespective of whether or not the patient has already been receiving treatment, it is advisable to adhere to the following dosage recommendations:

Initial treatment

Daily dose for 4 to 7 days (or at the most for 2 weeks) - 1 capsule.

Maintenance treatment (Normal dosage)

Daily dose - 1 capsule twice daily.

Maintenance treatment in exceptional cases

Daily dose - 1 capsule 3 times daily.

The purpose of the low initial dosage is to establish the patient's individual response to SYMMETREL. After 4 to 7 days it is usually possible to raise the dosage to the normal maintenance level.

The dose can be titrated against signs and symptoms. Dosages 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.

The higher maintenance dose for use in exceptional cases should be given only to patients who tolerate SYMMETREL well and who can be expected to benefit from a dosage in excess of the normal.

SYMMETREL acts within a few days but often appears to lose some of its efficacy within a few months of continuous treatment. The effectiveness of SYMMETREL may be prolonged

by a temporary withdrawal, which seems to restore activity. Treatment with SYMMETREL must be reduced gradually to avoid exacerbation of Parkinson's syndrome.

SYMMETREL can be given alone for initial therapy or combined with anticholinergic agents or levodopa.

Combined treatment

Any antiparkinsonian medicine that a patient may already be receiving should be continued during the first stage of treatment with SYMMETREL. In many cases it will then be possible to gradually taper off the dosage of the previous antiparkinsonian medicine without loss of benefits to the patient. If increased side effects occur, however, the dosage of the previous medicine should be reduced more quickly.

In patients already receiving high doses of anticholinergic medicines or L-dopa, the period of initial low-dosage treatment with SYMMETREL should preferably be extended to 2 weeks.

A Virus Influenza

Prophylaxis and treatment with SYMMETREL should be initiated as early as possible.

Children aged 5 to 9 years

1 capsule once daily.

Children and adults 10 to 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 “Dosage and directions for use – Use in elderly patients”.

Prevention

The 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, SYMMETREL is continued for two to three weeks after administration of the vaccine.

Treatment should be continued for 4 to 5 days. SYMMETREL should be started within 48 hours of symptoms appearing.

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.

Dosage in renal impairment

Careful adjustment of the dose of SYMMETREL by increasing the dosing interval according to creatinine clearance (see table) is required in patients with compromised renal function and under haemodialysis, following a loading dose of 200 mg on the first day.

Creatinine clearance [mL/(min. x 1,73 m^2)]	100 mg dose interval
< 15	7 days
15 to 25	3 days
25 to 35	2 days
35 to 75	1 day
> 75	12 hours

Side-effects and special precautions

SYMMETREL's side effects usually appear within the first 2 to 4 days of treatment and may disappear again after a few days, either spontaneously or following a reduction in the dosage or within 24 to 48 hours after discontinuation of amantadine.

Table of ADRs:

Blood and the lymphatic system disorders

Less frequent: Leucopenia

Metabolism and nutrition disorders

Less frequent: Anorexia

Psychiatric disorders

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

Less frequent: Depression, anxiety, elevation of mood, agitation, nervousness, hallucinations, nightmares, confusional state, disorientation, psychotic disorder.

Frequency unknown: Delirium, hypomanic state, mania.

Nervous system disorders

Less frequent: Disturbance in attention, dizziness, mild headache, insomnia, lethargy, ataxia, dysarthria, tremor, dyskinesia, convulsion, NMS-like symptom.

Eye disorders

Less frequent: Vision blurred, corneal lesions, e.g. punctuate corneal opacities which may be associated with superficial punctuate keratitis, corneal oedema, and markedly visual acuity.

Cardiac disorders

Less frequent: palpitations, heart failure.

Vascular disorders

Less frequent: Orthostatic hypotension.

Gastro-intestinal disorders

Less frequent: dry mouth, nausea, vomiting, constipation, diarrhoea.

Skin and subcutaneous tissue disorders

Frequent: Livedo reticularis

Less frequent: Hyperhidrosis, rash, photosensivity reaction, drug eruption.

Renal and urinary disorders

Less frequent: Urinary retention, urinary incontinence.

General disorders and administration site conditions

Frequent: Oedema peripheral

Investigations

Less frequent: Reversible liver function test abnormality.

In post-marketing exposure hypothermia has been reported in children mainly those younger than 5 years of age (see Warnings and Special Precautions). The frequency cannot be established.

Precautions

Medical supervision during treatment with SYMMETREL is essential.

When employing SYMMETREL in combination with other antiparkinson medicines, a watch should be kept for the latter's side-effects.

SYMMETREL may aggravate central nervous, gastro-intestinal, or other side-effects provoked by anticholinergic agents, or with L-dopa. During combined treatment with anticholinergic agents or with L-dopa attention should likewise be paid to the latter's contra-indications.

If a skin rash or any other symptoms develop during treatment, or if a patient has reason to suspect that she has become pregnant, the doctor should be informed without delay.

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. Although inconclusive, there is some evidence that SYMMETREL may exacerbate pre-existing congestive cardiac failure.

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 SYMMETREL are eliminated by patients undergoing haemodialysis for renal failure, these patients should have their dosage carefully adjusted in order to avoid adverse reactions (see Dosage and Directions for use).

SYMMETREL given in normal doses accumulates in patients with impaired renal function and leads to neurotoxic manifestations.

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 Dosage and directions for use).

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

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

Effects on ability to drive and use machines

Patients receiving SYMMETREL should be warned that dizziness, blurred vision and other central nervous symptoms may occur and impair the reaction of the patient, in which case they should not drive or use machines.

Known symptoms of overdosage and particulars of its treatment

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 ataxia, hyperexcitability tremors.

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, dysrhythmia, hypertension.

Gastro-intestinal system

Nausea, vomiting, dry mouth.

Renal function

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

Overdose from combined drug treatment

The peripheral and central adverse effects of anticholinergic agents are increased by the concomitant use of SYMMETREL, 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 SYMMETREL may be aggravated and/or modified.

Treatment

There is no specific antidote.

Treatment is symptomatic and supportive.

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 SYMMETREL 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.

For extreme cases forced diuresis, or dialysis should be considered.

Identification

Reddish-brown, opaque, shiny, oblong capsules, length: 15,4 mm, diameter: 5,8 mm. Imprinted in white, "GEIGY" on one side and "GB" on the other side.

Presentation

SYMMETREL is available as 100 mg capsules in packs of 20.

Storage instructions

Store below 25 °C and protect from heat and moisture.

KEEP OUT OF THE REACH OF CHILDREN.

Registration number

A/20.2.8/768

Name and business address of the holder of the certificate

NOVARTIS SOUTH AFRICA (Pty) Ltd

Magwa Crescent West

Waterfall City, Jukskei View

Johannesburg

2090

Date of publication of this package insert

11 February 2011

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Namibia: 90/20.2.8/00724	NS2

Manufacturer:

Catalent Germany Eberbach GmbH, Gammelsbacher Strasse 2, 69412 Eberbach, Germany