NOVARTIS

Symmetrel®

Antiparkinsonian agent and anti-influenzal virostatic

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Soft capsules.

Active substance

Each soft capsule contains 100 mg amantadine hydrochloride

Active moiety

Amantadine

Excipients

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

Preservatives in the capsule shell: sodium ethyl- and sodium propyl parahydroxybenzoate (E215, E217).

The capsule shell also contains: gelatin, glycerin, iron oxide red, sorbit, titanium dioxide.

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 INTERACTIONS).

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

- For individual and mass prophylaxis in subjects exposed to risk of infection, particularly when vaccination is unavailable or contraindicated;
- Prophylaxis in conjunction with inactivated vaccine during an outbreak until protective antibodies develop

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

Among pediatric patients, Symmetrel is indicated only in children aged 5 years and above.

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

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Parkinson's disease

Initially 100 mg per day, increased after one week to 200 mg per day in 2 divided doses. The dose can be titrated against signs and symptoms. Amounts exceeding 200 mg daily (up to maximum of 300 mg daily in divided doses) 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 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 WARNINGS AND PRECAUTIONS).

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

Combined treatment: Other 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 to gradually reduce the dosage of the other medication 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.

Drug-induced Parkinsonism

When management of Drug Induced Parkinsonism through dose reduction of causative drug is not practical, Symmetrel can be initiated at 100 mg twice daily. Treatment with Symmetrel may be reduced when the extra pyramidal symptoms are under control for a period of time.

Type A virus influenza - prevention and treatment

Adults (aged 19-65 years): 200 mg per day in 2 divided doses. .

Effective prevention and treatment of influenza A have been reported with a dosage of 100 mg daily (In case of intolerance to 200 mg per day, a dose of 100 mg daily could be used).

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 should be 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 onset of symptoms, the duration of fever and other effects is reduced by 1 day and the inflammatory reaction of the minor bronchial tree that usually accompanies influenza resolves more quickly.

Special populations

Pediatric patients(below 18 years)

Type A virus influenza – Prevention and treatment:

Children aged 5 to 9 years: 100 mg per day as a single dose.

Children aged 10 to 18 years: 200 mg per day in 2 divided doses.

Geriatric patients (65 years or above)

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 dosing interval should be adjusted (see section DOSAGE REGIMEN AND ADMINISTRATION - Renal impairment).

Renal impairment

In patients with compromised renal function and under hemodialysis 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 to creatinine clearance (see table 1) is required in these patients.

For patients with compromised renal function treated for influenza A infection a loading dose of Symmetrel 200 mg should be administered on the first day. For patients with compromised renal function being initiated treatment with Symmetrel for Parkinson's disease, a loading dose of 100 mg/day should be used on the first day.

Dose thereafter: 100mg at interval shown below

Table 1 Creatinine clearance at 100 mg dose interval

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

For the patients on hemodialysis a maintenance dose of 100 mg should be given once every 7 days (i.e. once in a week) starting from the 8^{th} day.

Ideally, plasma amantadine concentrations should be monitored. Careful surveillance of the patient is recommended (see section Clinical Pharmacology/Pharmacokinetics/Special populations).

Method of administration

The capsules should be taken orally with food to avoid gastric irritation.

CONTRAINDICATIONS

- Pregnancy;
- Known hypersensitivity to amantadine or to any of the excipients of Symmetrel.

WARNINGS AND PRECAUTIONS

Patients with pre-existing seizure disorders have been reported to develop an increased frequency of generalized seizures during amantadine therapy. A reduction in dosage may minimize 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 risks outweigh the benefits of treatment. A small number of suicide attempts, some of which were fatal, have been reported during treatment with amantadine. Because some patients have also attempted suicide by using an overdose of amantadine, prescriptions should be written for the smallest quantity consistent with good patient management.

Peripheral edema 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 required 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 hemodialysis for renal failure, these patients should have their dosage carefully adjusted in order to avoid adverse reactions (see section DOSAGE REGIMEN AND ADMINISTRATION and section OVERDOSAGE).

Hypothermia has been observed in children. Caution should be exercised when prescribing Symmetrel to children for the prevention and treatment of influenza type A virus illness (see also section DOSAGE REGIMENAND ADMINISTRATION).

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

If blurred vision or other visual problems occur, an ophthalmologist should be contacted to exclude corneal edema. In case that corneal edema is diagnosed, treatment with amantadine should be discontinued.

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), catatonia as well as in cognitive manifestations (e.g. confusion, disorientation, worsening of mental status, delirium). There have been isolated reports of a possible association between the occurrence or 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.

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Symmetrel. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

Driving and using machines

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

ADVERSE DRUG REACTIONS

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 common adverse drug reactions (particularly affecting the central nervous system) with increasing doses.

Adverse drug reactions from clinical trials, spontaneous reports and literature cases (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Adverse drug reactions

Nervous system disorders	
Uncommon**:**	Dizziness, headache, lethargy, ataxia, dysarthria
Rare:	Tremor, dyskinesia, convulsion
Very rare:	NMS-like symptoms
Psychiatric disorders	
Uncommon:	Depression, anxiety, elevated mood, agitation, nervousness, insomnia, hallucinations, nightmares. 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:	Confusional state, disorientation, psychotic disorder Delirium, hypomania and mania have been reported but their incidence cannot be readily deduced from the literature.
Eye disorders	
Uncommon:	Vision blurred
Rare:	Corneal lesions, e.g. punctate sub epithelial opacities which might be associated with superficial punctate keratitis, corneal epithelial edema, and markedly reduced visual acuity.
General disorders and administration site conditions	
Common:	Oedema peripheral In post-marketing exposure hypothermia has been reported in children (see also section WARNINGS AND PRECAUTIONS). The frequency can not be established
Skin and subcutaneous tissue disorders	
Common:	Livedo reticularis
Uncommon:	Hyperhidrosis
Rare:	Rash
Very rare:	Photosensitivity reaction
Cardiac disorders	
Uncommon:	Palpitations
Very rare:	Cardiac failure
Vascular disorders	
Uncommon:	Orthostatic hypotension
Blood and lymphatic system disorders	
Very rare:	Leukopenia
Investigations	
Very rare:	Reversible elevation of liver enzymes
Gastrointestinal disorders	

Uncommon:	Dry mouth, nausea, vomiting, constipation
Rare:	Diarrhea
Metabolism and nutrition disorders	
Uncommon:	Decreased appetite
Renal and urinary disorders	
Rare:	Urinary retention, urinary incontinence

Additional adverse drug reactions from spontaneous reports and literature cases (frequency not known)

Impulse control disorders

Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Symmetrel (see section WARNINGS AND PRECAUTIONS).

INTERACTIONS

Observed interactions resulting in concomitant use not being recommended

Co-administration of amantadine with a fixed dose combination of hydrochlorothiazide and triamterene may reduce the systemic clearance of the drug leading to increased plasma concentrations and toxic effects (confusion, hallucinations, ataxia, myoclonus).

In isolated cases psychotic decompensation has been reported in patients receiving amantadine and concomitant antipsychotic drugs or levodopa. Co-administration of amantadine and anticholinergic agents or levodopa may increase confusion, hallucinations, nightmares, gastrointestinal disturbances, or other atropine-like side effects (see section OVERDOSAGE).

Anticipated interactions to be considered

Drugs acting on the central nervous system

Concomitant t 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 OVERDOSAGE).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

Symmetrel is contraindicated during pregnancy. Amantadine-related complications during pregnancy have been reported

Animal data

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

Lactation

Risk Summary

Amantadine is transferred into breast milk. Adverse drug reactions have been reported in breast-fed infants. Nursing mothers should not take Symmetrel.

Females and males of reproductive potential

Females of child-bearing potential must use effective contraception(methods that result in less than 1 % pregnancy rates) during treatment, and for 5 days after their last dose of amantadine.

Infertility

Symmetrel at a dose of 32 mg/kg/day (equal to the maximum recommended human dose on a mg/m^2 basis) administered to both male and female rats impaired fertility (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

Overdose (acute overdose with multiples of the maximum recommended dose or overexposure due to high dosages for elderly and/or renally impaired patients) with Symmetrel can lead to fatal outcome (see section WARNINGS AND PRECAUTIONS).

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, aggression/hostility, depressed level of consciousness and coma.

Respiratory system

Hyperventilation, pulmonary edema, 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 the 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 favors the excretion of amantadine in the urine. Hemodialysis does not remove significant amounts of Symmetrel; in patients with renal failure, 4-hour hemodialysis 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. Caution is required when administering adrenergic substances in case of cardiac arrhythmias and hypotension as the clinical status may deteriorate due to the arrhythmogenic nature of the adrenergic drugs.

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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group

Antiparkinsonian agent and anti-influenzal virostatic.

ATC code

N04B B01.

Mechanism of action (MOA)/ pharmacodynamics (PD)

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 improves both the cardinal signs and symptoms of parkinsonism and functional capacity.

The effect generally sets in 2 to 5 days after the start of treatment. It exerts a positive effect, particularly on akinesia, rigidity, and tremor.

As an 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 micrograms/mL or less of amantadine. The exact mechanism of the antiviral activity of Amantadine has not been fully elucidated. Amantadine blocks the ion channel activity of M2 viral protein in the influenza virus through allosteric inhibition and as a result viral uncoating cannot take place. This eventually inhibit viral replication. Effects on late replicative steps with impaired assembly of virus have been found for certain avian influenza viruses.

Pharmacokinetics (PK)

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 / metabolism

Amantadine is metabolized to a minor extent and 8 metabolites of the drug have been identified. The major metabolite, the N-acetylated metabolite, accounts for 5-15% of the administered dose. The pharmacological efficacy or toxicity of metabolites is not known. Although the impact of the individual's acetylator status on the metabolism of the drug is not studied extensively, studies indicate that there is no correlation between NAT1 & NAT2 acetylator phenotype and amantadine acetylation.

Elimination

Amantadine 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 creatinine clearance, suggesting renal tubular secretion.

A single dose of amantadine is excreted over 72 hours as follows: 65-85% unchanged, 5-15% as an acetyl metabolite in urine, and 1% in feces. After 4-5 days 90% of the dose appears unchanged in urine. The pH of urine has significant impact on the rate of elimination and increase in urine pH may lead to a considerable decrease in the rate of elimination of amantadine.

Dose proportionality

Amantadine exhibits dose-proportionate pharmacokinetics over a dose range of 100 to 200mg.

Special populations

Gender effect

A few studies indicate the possibility of higher renal clearance of amantadine in men than in women.

Geriatric patients

Compared with data from healthy young adults, the half-life is doubled, and renal clearance is diminished. The renal/creatinine clearance ratio in elderly subjects is lower than in young people. In general, tubular secretion is more reduced than glomerular filtration in the elderly. In elderly patients with renal function impairment repeated administration of 100 mg daily for 14 days increase the plasma concentration into the toxic range.

Renal impairment

As amantadine is primarily excreted through the kidneys, it may accumulate in patients with renal impairment. A creatinine clearance of less than 40 mL/[min. 1.73 m^2] causes a 3- to 5-fold increase in half-life 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 nanograms/mL.

Hemodialysis

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

Hepatic impairment

The impact of hepatic impairment on the pharmacokinetics of amantadine is not known. The major fraction of the administered dose of amantadine is excreted unchanged in the urine and only a small fraction of drug undergoes metabolism in liver (see Biotransformation/metabolism above) .

Food effect

Food has no significant impact on the pharmacokinetics of amantadine. A slight delay in the onset of absorption may be observed after the administration of Symmetrel with food.

Ethnic sensitivity

Although the impact of ethnic sensitivity and race on the pharmacokinetics of amantadine has not been studied extensively, the disposition of amantadine is not known to be governed by genetic factors (see Biotransformation/metabolism above).

Clinical studies

Symmetrel is an established product. No recent clinical studies have been conducted.

NON-CLINICAL SAFETY DATA

Amantadine hydrochloride exhibited a low degree of acute toxicity in mice, rats, guinea pigs, dogs and monkeys. 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 2 years of oral doses up to 160 and 80 mg/kg, respectively, did not disclose specific toxicity.

Reproductive toxicity

(See section Pregnancy, lactation, females and males of reproductive potential).

Fertility

There are no GLP studies conducted according to current recommended methodology to assess effects of amantadine on fertility. In a three litter, non-GLP, reproduction study in rats, Symmetrel at a dose of 32 mg/kg/day (equal to the maximum recommended human dose on a mg/m^2 basis) administered to both males and females impaired fertility. There were no effects on fertility at a dose level of 10 mg/kg/day (or 0.3 times the maximum recommended human dose on a mg/m^2 basis); intermediate doses were not tested.

Mutagenicity

In vitro and *in vivo* studies indicate that amantadine is not mutagenic. Long-term *in vivo* animal studies evaluating the carcinogenic potential of amantadine have not been performed.

Carcinogenicity

No evidence of a carcinogenic effect was found in a 2-year oral toxicity study in rats. However, the number of animals per dose group used in this study was not sufficient to fully evaluate carcinogenic potential.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

Symmetrel should not be used after the date marked “EXP” on the pack.

INSTRUCTIONS FOR USE AND HANDLING

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

Manufacturer:

See folding box.

Country Specific Package Leaflet

Information issued: Apr 2019.SIN

® = registered trademark

Novartis Pharma AG, Basel, Switzerland