

# NEW ZEALAND DATA SHEET

## **SYMMETREL<sup>®</sup>** **Amantadine Hydrochloride** **100 mg Soft Capsules**

### **Qualitative and quantitative composition**

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

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

### **Pharmaceutical form**

Reddish-brown oblong capsule approximately 15mm long containing 100mg amantadine hydrochloride. One side is branded GEIGY and the second side is branded GB. The branding is white in colour.

### **Clinical particulars**

#### **Indications**

##### **Treatment of Parkinson's disease**

- Idiopathic parkinsonism,
- Secondary parkinsonism (e.g. of post-encephalitic type, of cerebrovascular origin or drug-induced parkinsonism) (see Interactions).

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

##### **Treatment of infection and prevention 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.

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.

Among paediatric 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 and Administration**

##### **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 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 Warnings and Precautions for use).

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 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**

Adults: 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 tolerance to 200 mg per day, the 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 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 day and the inflammatory reaction of the minor bronchial tree that usually accompanies influenza resolves more quickly.

### **Paediatric patients**

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

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

### **Geriatric 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 dosing interval should be adjusted (see dosage in Renal impairment).

### **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 of 200 mg on the first day.

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

The recommended dosage for patients on haemodialysis is 200 mg every 7 days. Ideally, plasma amantadine concentrations should be monitored. Careful surveillance of the patient is recommended (see Pharmacokinetic properties).

## **Method of Administration**

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 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 by using an overdose of 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 of toxicity (see Dosage and administration and 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 (see also Dosage and administration).

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

## **Class effect**

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including Symmetrel, especially at high doses. These are generally reversible upon reduction of the dose or treatment discontinuation.

## **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 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.

## **Interactions**

### **Observed interactions resulting in a concomitant use not recommended**

Concomitant administration of amantadine with 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, and myoclonus).

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

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

### **Anticipated interactions to be considered**

#### **Drugs acting on central nervous system**

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 Overdose).

## **Pregnancy and Breast-feeding**

### **Pregnancy**

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

### **Breast-feeding**

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

### **Effects on ability to drive and use machines**

Patients receiving Symmetrel should be warned that dizziness, blurred vision and other central nervous symptoms (see 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 adverse 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 are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

### **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: confusion, disorientation, psychosis

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

#### **Cardiac disorders**

Uncommon: palpitations

Very rare: heart insufficiency/failure.

#### **Vascular disorders**

Uncommon: orthostatic hypotension

#### **Blood and lymphatic system disorders**

Very rare: leukopenia

#### **Gastrointestinal disorders**

Uncommon: dry mouth, nausea, vomiting, constipation.

Rare: diarrhoea.

#### **Skin and subcutaneous tissue disorders**

Common: livedo reticularis

Uncommon: diaphoresis.

Rare: exanthema.

Very rare: photosensitivity

#### **Eye disorders**

Uncommon: vision blurred

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

#### **Metabolism and nutrition disorders**

Uncommon: anorexia

#### **Renal and urinary disorders**

Rare: urinary retention, urinary incontinence.

#### **Investigations**

Very rare: reversible elevation of liver enzymes

#### **General disorders and administration site conditions**

In post-marketing exposure hypothermia has been reported in children (see Warnings and precautions). The frequency can not be established.

#### **Class effect:**

Patients treated with dopamine agonists for treatment of Parkinson's disease, including Symmetrel, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.

#### **Overdose**

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 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 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. Caution is required when administering adrenergic substances in case of cardiac arrhythmias and hypotension as the clinical status may deteriorate due to 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**

#### **Pharmacodynamic properties**

Pharmacotherapeutic group: Antiparkinsonian agent and anti-influenzal virostatic

#### **ATC code**

N04B B01

#### **Mechanism of action (MOA)/ Pharmacodynamics**

##### **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<sub>1</sub>N<sub>1</sub>, H<sub>2</sub>N<sub>2</sub>, H<sub>3</sub>N<sub>2</sub> subtypes, are inhibited by 0.4 micrograms/mL or less of amantadine. Amantadine effectively 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 results in inhibition of viral replication. Effects on late replicative steps with impaired assembly of virus have been found for certain avian influenza viruses.

### **Pharmacokinetic properties**

#### **Absorption**

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

Following repeated administration of 25, 100, or 150 mg twice daily the steady-state plasma concentration of 110, 302, or 588 nanograms/mL respectively are attained within 3 days.

#### **Distribution**

*In vitro*, approximately 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.

Amantadine accumulates in nasal secretions after several hours.

Amantadine crosses the blood-brain barrier and the elimination half-life of amantadine from brain tissue (6.5 days) is much longer than from blood. The mean cerebrospinal fluid (CSF) to serum ratio for total amantadine is about 0.76.

#### **Metabolism**

Amantadine is metabolized to a minor extent and eight metabolites of amantadine have been identified. The major metabolite, N-acetylated metabolite, accounts for 5-15 % of the administered dose. The pharmacological activity of metabolites is not known. The impact of the individual's acetylator status on the metabolism of amantadine is not well established.

#### **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 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 pH of urine has significant impact on the rate of elimination and increase in urine pH may lead to considerable decrease in the rate of elimination of amantadine.

## **Dose proportionality**

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

## **Special populations**

### **Gender effect**

A few studies indicate the possibility of higher renal clearance of amantadine in males compared to females.

### **Elderly patients**

Compared with data from healthy young adults, the  $t_{1/2}$  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 impairment**

As amantadine is primarily excreted through the kidneys, the accumulation of amantadine may occur in patients with renal impairment. A creatinine clearance of less than 40 mL/[min.  $1.73 \text{ m}^2$ ] 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.

### **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 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 metabolism in pharmacokinetics section).

### **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 metabolism in pharmacokinetics section).

## **Clinical studies**

Symmetrel is an established product.

## **Non-clinical 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.

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

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

### **Pharmaceutical information**

#### **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.

#### **Incompatibilities**

Not applicable.

#### **Special precautions for storage**

Protect from moisture and heat (Store at or below 25°C).

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

#### **Nature and contents of container**

Bottles containing 60 capsules

#### **Medicine classification**

Prescription Medicine

#### **Name and address**

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#### **Date of preparation**

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