NEW ZEALAND DATA SHEET

1 PRODUCT NAME

SYMMETREL 100 mg capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains amantadine hydrochloride 100 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

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

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 *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.

4.2 Dose and method of administration

Dosage

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*).

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 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.

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.

Special populations

Paediatric patients

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 (aged 65 years and 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, or develops, 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 to the creatinine

clearance (see table 1) is required in these patients, following a loading dose on the first day of treatment with Symmetrel equivalent to the initial dose for patients without renal impairment:

Type A influenza:	200 mg for adults, and children 10 to 18 years old; 100 mg for children 5 to 9 years old, and adults 65 years and older
Parkinson's disease:	100 mg

Table 1:

Creatinine clearance [mL/(min 1.73 m^2)]	100 mg dose interval
< 15	7 days
15-25	3 days
26-35	2 days
36-75	1 day
> 75	12 hours

For patients on haemodialysis, the maintenance dose of 100 mg should be taken once every 7 days (i.e. once a week), starting from the interval after the loading dose.

Ideally, plasma amantadine concentrations should be monitored. Careful surveillance of the patient is recommended (see *Further information: Pharmacokinetics*).

Method of Administration

Capsules should be taken orally with food to avoid gastric irritation.

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 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 (see *Dosage and administration* and *Overdose*).

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.

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

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers 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.

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.

4.5 Interaction with other medicines and other forms of interaction

Observed interactions resulting in concomitant use not being recommended

Concomitant 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, 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 the 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*).

4.6 Fertility, pregnancy and lactation

Pregnancy and women of child-bearing potential

Amantadine-related complications during pregnancy have been reported. Symmetrel is contraindicated during pregnancy. Women of child-bearing potential must use highly effective contraception during treatment, and for 5 days after their last dose of amantadine.

Breast-feeding

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

Fertility

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 *Further information: non-clinical safety data*).

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 *Adverse drug reactions*) may occur and impair the reaction of the patient, in which case they should not drive or use machines.

4.8 Undesirable effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

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); not known (reported, but frequency cannot be established).

Table 2:

System organ class / frequency	Adverse drug reaction
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*
Rare	Confusional state*, disorientation, psychotic disorder
Not known	Delirium, hypomania, mania ** more frequently reported when amantadine is administered concurrently with anticholinergic agents or when the patient has an underlying psychiatric disorder.*
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
General disorders and administration site conditions	
Common	Oedema peripheral
Not known	Hypothermia (reported in children, see *Warnings and precautions*)
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

System organ class / frequency	Adverse drug reaction
Gastrointestinal disorders	
Uncommon	Dry mouth, nausea, vomiting, constipation
Rare	Diarrhoea
Metabolism and nutrition disorders	
Uncommon	Decreased appetite
Renal and urinary disorders	
Rare	Urinary retention, urinary incontinence

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 *Warnings and precautions*).

4.9 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 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 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 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 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_1N_1, H_2N_2, H_3N_2 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.

Clinical efficacy and safety

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

5.2 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.

Biotransformation/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 the 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 men than in women.

Geriatric 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 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.

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 *Biotransformation/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 *Biotransformation/Metabolism* in *Pharmacokinetics* section).

5.3 Preclinical 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 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. 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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill: Rape oil; soybean lecithin; wax blend composed of one part yellow beeswax, one part hydrogenated soya bean oil, four parts partially hydrogenated soya bean oil.

Capsule shell: gelatin, glycerol, sorbitol special blend with mannitol and hydrolysed starch (Karion 83), iron oxide red, titanium dioxide, sodium ethyl hydroxybenzoate, sodium propyl hydroxybenzoate, printing ink-white.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 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.

6.5 Nature and contents of container

Bottles containing 60 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Novartis New Zealand Limited
PO Box 99102
Newmarket
Auckland 1149

Telephone: 0800 354 335

9 DATE OF FIRST APPROVAL

31 December 1969

10 DATE OF REVISION OF THE TEXT

08 September 2020

SUMMARY TABLE OF CHANGES

Section	Summary of changes
Section 8 - SPONSOR	Removed Sponsor's old address.

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