SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Symmetrel capsules 100mg

Amantadine hydrochloride 100mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Amantadine hydrochloride PhEur 100mg.

3 PHARMACEUTICAL FORM

Brownish-red, hard gelatin capsules imprinted SYMM in white on both cap and body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

*Parkinson's disease.*

*Herpes zoster.* It is recommended that Symmetrel/Amantadine be given to elderly or debilitated patients in whom the physician suspects that a severe and painful rash could occur. Symmetrel/Amantadine can significantly reduce the proportion of patients experiencing pain of long duration.

4.2 Posology and method of administration

*Parkinson's disease:* Initially 100mg daily for the first week, increasing to 100mg twice daily. The dose can be titrated against signs and symptoms. Doses exceeding 200mg daily may provide some additional relief, but may also be associated with increasing toxicity. A dose of 400mg/day should not
be exceeded. The dose should be increased gradually, at intervals of not less
than 1 week. Since patients over 65 years of age tend to show lower renal
clearance and consequently higher plasma concentrations, the lowest effective
dose should be used.

Amantadine acts within a few days, but may appear to lose efficacy within a
few months of continuous treatment. Its effectiveness may be prolonged by
withdrawal for three to four weeks, which seems to restore activity. During
this time, existing concomitant antiparkinsonian therapy should be continued,
or low dose L-dopa treatment initiated if clinically necessary.

Symmetrel/Amantadine withdrawal should be gradual, e.g. half the dose at
weekly intervals. Abrupt discontinuation may exacerbate Parkinsonism,
regardless of the patient’s response to therapy (see Section 4.4, “Special
warnings and precautions for use”). Combined treatment: any antiparkinson
drug already in use should be continued during initial Symmetrel/Amantadine
treatment. It may then be possible to reduce the other drug gradually. If
increased side effects occur, the dosage should be reduced more quickly. In
patients receiving large doses of anticholinergic agents or L-dopa, the initial
phase of Symmetrel/Amantadine treatment should be extended to 15 days.

**Herpes zoster:** 100mg twice daily for 14 days. Treatment should be started as
soon as possible after diagnosis. If post-herpetic pain persists treatment can be
continued for a further 14 days.

In patients with **renal impairment:** the dose of amantadine should be reduced.
This can be achieved by either reducing the total daily dose, or by increasing
the dosage interval in accordance with the creatinine clearance. For example,

<table>
<thead>
<tr>
<th>Creatinine clearance ml/(min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>Symmetrel/Amantadine contra-</td>
</tr>
<tr>
<td></td>
<td>indicated.</td>
</tr>
<tr>
<td>15 – 35</td>
<td>100mg every 2 to 3 days.</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>100mg every day</td>
</tr>
</tbody>
</table>

*The above recommendations are for guidance only and physicians should continue to monitor their patients for signs of unwanted effects.*

### 4.3 Contraindications

Known hypersensitivity to amantadine or any of the excipients. Individuals subject to

### 4.4 Special warnings and precautions for use
Symmetrel/Amantadine should be used with caution in patients with confusional or hallucinatory states or underlying psychiatric disorders, in patients with liver or kidney disorders, and those suffering from, or who have a history of, cardiovascular disorders. Caution should be applied when prescribing amantadine with other medications having an effect on the CNS (See section 4.5, Interactions with other medicaments and other forms of interaction).

Abrupt discontinuation of amantadine may result in worsening of Parkinsonism or in symptoms resembling neuroleptic malignant syndrome (NMS), as well as in cognitive manifestations (e.g. catatonia, confusion, disorientation, worsening of mental status, delirium). Symmetrel/Amantadine should not be stopped abruptly in patients who are treated concurrently with neuroleptics. There have been isolated reports of precipitation or aggravation of neuroleptic malignant syndrome or neuroleptic-induced catatonia following the withdrawal of amantadine in patients taking neuroleptic agents. A similar syndrome has also been reported rarely following withdrawal of amantadine and other anti-parkinson agents in patients who were not taking concurrent psychoactive medication.

As some individuals have attempted suicide with amantadine, prescriptions should be written for the smallest quantity consistent with good patient management.

Peripheral oedema (thought to be due to an alteration in the responsiveness of peripheral vessels) may occur in some patients during chronic treatment (not usually before four weeks) with Symmetrel/Amantadine. This should be taken into account in patients with congestive heart failure.

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

### 4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of amantadine and anticholinergic agents or levodopa may increase confusion, hallucinations, nightmares, gastro-intestinal disturbances, or other atropine-like side effects (see Section 4.9 “Overdose”). Psychotic reactions have been observed in patients receiving amantadine and levodopa.

In isolated cases, worsening of psychotic symptoms has been reported in patients receiving amantadine and concomitant neuroleptic medication.

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

There have been isolated reports of a suspected interaction between amantadine and combination diuretics (hydrochlorothiazide + potassium sparing diuretics). One or both of the components apparently reduce the clearance of amantadine, leading to higher plasma concentrations and toxic effects (confusion, hallucinations, ataxia, myoclonus).
4.6 Fertility, Pregnancy and lactation

Amantadine-related complications during pregnancy have been reported. Symmetrel/Amantadine is contra-indicated during pregnancy and in women trying to become pregnant. Amantadine passes into breast milk. Undesirable effects have been reported in breast-fed infants. Nursing mothers should not take Symmetrel/Amantadine.

4.7 Effects on ability to drive and use machines

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness or blurred vision.

4.8 Undesirable effects

Amantadine's undesirable effects are often mild and transient, usually appearing within the first 2 to 4 days of treatment and promptly disappearing 24 to 48 hours after discontinuation. A direct relationship between dose and incidence of side effects has not been demonstrated, although there seems to be a tendency towards more frequent undesirable effects (particularly affecting the CNS) with increasing doses.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (greater than or equal to 1 in 10); common (less than or equal to 1 in 100, less than 1 in 10); uncommon (greater than or equal to 1 in 1,000, less than 1 in 100); rare (greater than or less than 1 in 10,000, less than 1 in 1,000) very rare (less than 1 in 10,000), not known (where no valid estimate of the incidence has been derived).

NB: The incidence and severity of some of the adverse reactions, noted below, varies according to the dosage and nature of the disease under treatment.

Table 1
Blood and lymphatic system disorders:
Very rare: leucopenia, reversible elevation of liver enzymes

Nervous system disorders:
Common: anxiety, elevation of mood, lightheadedness, headache, lethargy, hallucinations, nightmares, ataxia, slurred speech, blurred vision, loss of concentration, nervousness, depression, insomnia, myalgia. Hallucinations, confusion and nightmares ¹
Uncommon: confusion, disorientation, psychosis, tremor, dyskinesia, convulsions, neuroleptic malignant-like syndrome
Not known: Delirium, hypomanic state and mania ²

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

Cardiac disorders:
Very common: oedema of ankles, livedo reticularis ³
Common: palpitations, orthostatic hypotension
Very rare: heart insufficiency/failure

Gastrointestinal disorders:
Common: dry mouth, anorexia, nausea, vomiting, constipation
Rare: diarrhoea

Skin and subcutaneous tissue disorders:
Common: diaphoresis.
Rare: exanthema
Very rare: photosensitisation

Renal and urinary disorders:
Rare: urinary retention, urinary incontinence

¹ more common when amantadine is administered concurrently with anticholinergic agents or when the patient has an underlying psychiatric disorder.

² reported but their incidence cannot be readily deduced from the literature.

³ usually after very high doses or use over many months.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal
product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (Website: www.mhra.gov.uk/yellowcard).

4.9 Overdose

Overdose with Symmetrel/Amantadine can lead to fatal outcome.

**Signs and symptoms:** Neuromuscular disturbances and symptoms of acute psychosis are prominent. **Central nervous system:** Hyperreflexia, motor restlessness, convulsions, extrapyramidal signs, torsion spasms, dystonic posturing, dilated pupils, dysphagia, confusion, disorientation, delirium, visual hallucinations, myoclonus. **Respiratory system:** hyperventilation, pulmonary oedema, respiratory distress, including adult respiratory distress syndrome. **Cardiovascular system:** cardiac arrest and sudden cardiac death have been reported. Sinus tachycardia, arrhythmia, hypertension. **Gastrointestinal system:** nausea, vomiting, dry mouth. **Renal function:** urine retention, renal dysfunction, including increase in BUN and decreased creatinine clearance.

*Overdose from combined drug treatment:* the effects of anticholinergic drugs are increased by amantadine. Acute psychotic reactions (which may be identical to those of 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. Induction of vomiting and/or gastric aspiration (and lavage if patient is conscious), activated charcoal or saline cathartic may be used if judged appropriate. Since amantadine is excreted mainly unchanged in the urine, maintenance of renal function and copious diuresis (forced diuresis if necessary) are effective ways to remove it from the blood stream. Acidification of the urine favours its excretion. Haemodialysis does not remove significant amounts of amantadine.

Monitor the blood pressure, heart rate, ECG, respiration and body temperature, and treat for possible hypotension and cardiac arrhythmias, as necessary. **Convulsions and excessive motor restlessness:** administer anticonvulsants such as diazepam iv, paraldehyde im or per rectum, or phenobarbital im. **Acute psychotic symptoms, delirium, dystonic posturing, myoclonic manifestations:** physostigmine by slow iv infusion (1mg doses in adults, 0.5mg in children) repeated administration according to the initial response and the subsequent need, has been reported. **Retention of urine:** bladder should be catheterised; an indwelling catheter can be left in place for the time required.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiparkinsonian agent

ATC code N04B B01

*Parkinson's disease:* Symmetrel/Amantadine has been shown to be a low affinity antagonist at the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors. Overactivity of glutamatergic neurotransmission has been implicated in the generation of parkinsonian symptoms. The clinical efficacy of amantadine is thought to be mediated through its antagonism at the NMDA subtype of glutamate receptors. In addition, amantadine may also exert some anticholinergic activity.

*Herpes Zoster:* The mechanism of action of Symmetrel/Amantadine in herpes zoster has not been fully characterised.

5.2 Pharmacokinetic properties

Absorption: Amantadine is absorbed slowly but almost completely. Peak plasma concentrations of approximately 250ng/ml and 500ng/ml are seen 3 to 4 hours after single oral administration of 100mg and 200mg amantadine, respectively. Following repeated administration of 200mg daily, the steady-state plasma concentration settles at 300ng/ml within 3 days.

Distribution: Amantadine accumulates after several hours in nasal secretions and crosses the blood-brain barrier (this has not been quantified). In vitro, 67% is bound to plasma proteins, with a substantial amount bound to red blood cells. The concentration in erythrocytes in normal healthy volunteers is 2.66 times the plasma concentration. The apparent volume of distribution is 5 to 10L/kg, suggesting extensive tissue binding. This declines with increasing doses. The concentrations in the lung, heart, kidney, liver and spleen are higher than in the blood.

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

Elimination: The drug is eliminated in healthy young adults with a mean plasma elimination half-life of 15 hours (10 to 31 hours). The total plasma clearance is about the same as renal clearance (250ml/min). The renal amantadine clearance is much higher than the creatinine clearance, suggesting renal tubular secretion. After 4 to 5 days, 90% of the dose appears unchanged in urine. The rate is considerably influenced by urinary pH: a rise in pH brings about a fall in excretion.

Characteristics in special patient populations:

Elderly patients: compared with healthy young adults, the half-life may be doubled and renal clearance diminished. Tubular secretion diminishes more than glomerular filtration in the elderly. In elderly patients with renal impairment, repeated administration of 100mg daily for 14 days raised the plasma concentration into the toxic range.
Renal impairment: amantadine may accumulate in renal failure, causing severe side effects. The rate of elimination from plasma correlates to creatinine clearance divided by body surface area, although total renal elimination exceeds this value (possibly due to tubular secretion). The effects of reduced kidney function are dramatic: a reduction of creatinine clearance to 40ml/min may result in a five-fold increase in elimination half-life. The urine is the almost exclusive route of excretion, even with renal failure, and amantadine may persist in the plasma for several days. Haemodialysis does not remove significant amounts of amantadine, possibly due to extensive tissue binding.

5.3 Preclinical safety data

Reproductive toxicity studies were performed in rats and rabbits. In rat oral doses of 50 and 100 mg/kg proved to be teratogenic. The maximum recommended dose of 400mg is less than 6mg/kg.

There are no other pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, polyvinylpyrrolidone, magnesium stearate, red iron oxide (E172), titanium dioxide (E171), gelatin and monogramming ink S-1-7085 white containing titanium dioxide (E171), ammonium hydroxide 28%, propylene glycol (E1520), simethicone, or SB-0007P white ink containing: shellac, propylene glycol, sodium hydroxide, povidone, titanium dioxide (E171).

6.2 Incompatibilities

None known.

6.3 Shelf life

Five years.
6.4 **Special precautions for storage**

Protect from moisture. Medicines should be kept out of reach of children.

6.5 **Nature and contents of container**

Aluminium/PVdC blister packs of 28 or 56 capsules. Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

None.

7 **MARKETING AUTHORISATION HOLDER**

Auden Mckenzie (Pharma Division) Ltd
Whiddon Valley,
Barnstaple,
North Devon,
EX32 8NS,
United Kingdom.

8 **MARKETING AUTHORISATION NUMBER(S)**

PL 17507/0242

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26/06/1998
DATE OF REVISION OF THE TEXT

18/04/2016