SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amantadine Hydrochloride 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg Amantadine hydrochloride

Excipients with known effect:

Each capsule contains 20 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Size ‘‘4’’ plain hard gelatin capsules with brownish-red colored cap and body, contains white to off white granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Parkinson's disease.

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

4.2 Posology and method of administration

Posology

Parkinson's disease: Initially 100 mg daily for the first week, increasing to 100 mg twice daily. The dose can be titrated against signs and symptoms. Doses exceeding 200 mg daily may provide some additional relief, but may also be associated with increasing toxicity. A dose of 400 mg/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.

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 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 Amantadine treatment should be extended to 15 days.

Herpes zoster: 100 mg 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.

Renal impairment

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,

Creatinine clearance ml/(min)	Dose
< 15	Amantadine contra-indicated.
15 – 35	100 mg every 2 to 3 days.
> 35	100 mg every day

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

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Individuals subject to convulsions. A history of gastric ulceration. Severe renal disease. Pregnancy.

4.4 Special warnings and precautions for use

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).

Discontinuation of amantadine

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). 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.

Some individuals have attempted suicide and cases of suicidal ideation and behaviour have been reported during treatment with amantadine. Patients should be monitored for signs of suicidal ideation and behaviour and treatment initiated as needed. Patients (and caregivers of patients) should be advised to seek medical advice if any signs of suicidal ideation or behaviour emerge. 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 Amantadine. This should be taken into account in patients with congestive heart failure.

Anticholinergic effects

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 products with a dopaminergic effect, including amantadine. Dose reduction or tapered discontinuation should be considered if such symptoms develop.

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Pregnancy

Amantadine-related complications during pregnancy have been reported. Amantadine is contra-indicated during pregnancy and in women trying to become pregnant.

Breastfeeding

Amantadine passes into breast milk. Undesirable effects have been reported in breast-fed infants. Nursing mothers should not take 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

Summary of the safety profile

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.

Tabulated list of adverse reactions

The following list of adverse reactions is based on clinical trial experience and/or postmarketing use via spontaneous case reports and literature cases. The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as “not known”.

Undesirable effects are listed by MedDRA System Organ Classes. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Assessment of undesirable effects is based on the following frequency groupings:

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: cannot be estimated from the available data.

System Organ	Adverse Drug Reactions

Class	
Blood and lymphatic system disorders	*Very rare* leukopenia
Psychiatric disorders	*Common* depression, confusional state, hallucination, anxiety, euphoric mood, insomnia, nightmare*, nervousness
	Rare psychotic disorder, disorientation
	Not known impulse control disorders* (see section 4.4), delirium, hypomania, and mania
Nervous system disorders	*Common* dizziness, headache, lethargy, ataxia, disturbance in attention, dysarthria
	Rare Neuroleptic malignant syndrome, seizure (see section 4.4), dyskinesia, tremor
	Not known myoclonus
Eye disorders	*Uncommon* vision blurred
	Rare corneal lesion*, corneal oedema (see section 4.4), visual acuity reduced
Cardiac disorders	*Very common* oedema peripheral
	Common palpitations
	Very rare cardiac failure
Vascular disorders	*Common* orthostatic hypotension
Gastrointestinal disorders	*Common* dry mouth, decreased appetite, nausea, vomiting, constipation
	Rare diarrhoea

Skin and subcutaneous tissue disorders	*Very common* livedo reticularis*
	Common hyperhidrosis
	Rare rash
	Very rare photosensitivity reaction
Musculoskeletal and connective tissue disorders	*Common* myalgia
System Organ Class	**Adverse Drug Reactions**
Renal and urinary disorders	*Rare* urinary retention, urinary incontinence
Investigations	*Very rare* hepatic enzyme increased

*See section 'Description of selected adverse reactions'

Description of selected adverse reactions

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

Impulse control disorders: pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating, and compulsive eating can occur in patients with a dopaminergic effect including amantadine (see section 4.4 Special warnings and precautions for use).

Corneal lesions such as punctate subepithelial opacities which might be associated with superficial punctate keratitis.

Livedo reticularis can develop 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdose with Amantadine can lead to fatal outcome.

Signs and symptoms: *Neuromuscular* disturbances and symptoms of acute psychosis are prominent. *Central nervous system:* coma, 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 blood urea nitrogen 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 arhythmias, 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 (1 mg doses in adults, 0.5 mg 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

Mechanism of action

Parkinson's disease: Amantadine has been shown to be a low affinity antagonist at the Nmethyl-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 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 250 ng/ml and 500 ng/ml are seen 3 to 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

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 10 L/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 (250 ml/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

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 100 mg 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 40 ml/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 400 mg is less than 6 mg/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 monohydrate

Povidone

Magnesium stearate

Capsule cap & body

Iron oxide red (E 172)

Titanium dioxide (E 171)

Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/PVC/PVdC blister packs of 14 and 56 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20395/0416

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