SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amantadine hydrochloride 100 mg Capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100 mg Amantadine hydrochloride.

Excipient(s) with known effect

Each capsule also contains 15.20 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Hard gelatin capsule (size “4”, 14 mm), cavern pink cap printed “RENATA” in black and cavern pink body printed “AMCL” in black containing white crystalline 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).

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 contraindicated
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.

Paediatric population

There is no relevant use of Amantadine in the paediatric population

Method of administration

For oral use.

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).

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.

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 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.

Amantadine contains lactose, patient with rare hereditary problems of galactose intolerance, 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). 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).

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

contraindicated during pregnancy and in women trying to become pregnant.

Breast-feeding

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

Fertility

There are no human data on the effect of amantadine on fertility.

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.

List of adverse reactions

The frequencies of adverse events are ranked according to the following : 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).

Blood and lymphatic system disorders:	
Very rare:	Leucopenia, reversible elevation of liver enzymes
Psychiatric disorders:	
Not known:	Impulse control disorders[1]
Nervous system disorders:	
Common:	Anxiety, elevation of mood, light headedness, headache, lethargy, hallucinations, ataxia, slurred speech, loss of concentration, nervousness, depression, insomnia, myalgia. confusion and nightmares[2].
Rare:	Confusion, disorientation, psychosis, tremor, dyskinesia, convulsions, neuroleptic malignant-like syndrome
Not known:	Delirium, hypomanic state and mania[3].
Eye disorders:	
Uncommon	Blurred vision
Rare:	Corneal lesions, e.g. punctate sub epithelial 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[4].
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] 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 (see section "Special warnings and precautions for use").

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

[3] reported but their incidence cannot be readily deduced from the literature.

[4] 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: 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 (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: Anti-Parkinson Drug, ATC code: N04BB01

Mechanism of action

Parkinson's disease

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 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

Capsule Powder

Lactose monohydrate
Povidone
Magnesium stearate

Capsule shell

Gelatin
Iron oxide black (E172)
Iron oxide red (E172)
Titanium dioxide (E171)

Printing Ink

Shellac
Black iron oxide (E172)
Potassium hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu – PVC/PVdC blister pack containing 12(1 x 12 blister strips), 14 (1 x 14 blister strips), 24(2 x 12 blister strips), 28 (2 x 14 blister strips) and 56 (4 x 14 blister strips) 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

Renata (UK) Limited
Greenway Business Centre,
Harlow Business Park,
Harlow,
CM19 5QE,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 42765/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15/05/2025

10 DATE OF REVISION OF THE TEXT

15/05/2025