Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amantadine hydrochloride Renata 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

Symptomatic treatment of Parkinson's disease
Amantadine can be given as monotherapy at the start of treatment for Parkinson's disease or in combination with levodopa.

4.2 Posology and method of administration

Posology
Starting dose: 100 mg once daily after a meal, preferably in the morning.
Maintenance dose: 100 mg twice daily after meals.

The time interval between the starting dose and maintenance dose should be at least 7 days.
In individual cases, the dose can be further increased based on the clinical picture.
It is recommended to do this gradually at intervals of at least 1 week.
Administration must not be stopped abruptly (see section 4.4).

Combined treatment: If Amantadine is added to existing Parkinson's treatment, the lowest possible dose should be started and the dose should be titrated carefully and slowly.

Special populations

Paediatric population
Amantadine is not indicated for use in children.

Elderly (65 years and older)
Plasma amantadine concentrations are influenced by renal function. In the elderly, the elimination half-life is longer and renal clearance is less than in younger patients. Therefore, a maintenance dose not exceeding 100 mg per day is recommended in elderly patients without kidney disease. If the patient has renal impairment, the dosing interval should be adjusted (see below '*Patients with renal impairment*').

Patients with renal impairment
Clearance is significantly reduced in patients with renal impairment, resulting in increased plasma concentrations of amantadine. In these patients, the dosage should be adjusted with caution, by extending the dosing interval according to creatinine clearance (see Table 1), following a loading dose on day 1 of treatment.

If Parkinson's disease is diagnosed in a patient who already has impaired renal function (with or without haemodialysis), treatment should be started with a loading dose of 100 mg/day on day 1 of treatment. After the initial dose, the dosage interval should be followed according to the creatinine clearance (see Table 1).

If reduced renal function is observed in Parkinson's disease patients already receiving the maintenance dose of Amantadine (100 mg twice daily), the dosing interval can be switched immediately to the creatinine clearance-based dosing regimen (see Table 1), without a loading dose.

Table 1. 100 mg dosing interval based on creatine clearance

Creatinine clearance	**Dosing interval**
(ml/min/1.73m^2)	**100 mg**
< 15	7 days
15-25	3 days
25-35	2 days
35-75	1 day
> 75	12 hours

Monitoring of plasma levels is desirable. Careful monitoring of the patient is recommended (see sections 4.4 and 5.2 *'Characteristics in patients').*

Method of administration
For oral use.
The capsules should be taken with food to prevent stomach upset.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Refractory epilepsy.
- Psychoses.

4.4 Special warnings and precautions for use

It has been reported that patients with pre-existing epilepsy with seizures may develop an increase in the frequency of strong motor seizures during treatment with amantadine. A dose reduction can minimise this risk. These patients should be carefully monitored. Amantadine is contraindicated in refractory epilepsy.

Due to the severity of side effects with overdose, caution should be exercised in prescribing Amantadine to patients at increased risk of suicidal behaviour. These patients should be prescribed the smallest possible amount consistent with good patient treatment.

Peripheral oedema may occur during treatment with Amantadine, probably due to local vascular disturbances. This should be taken into account in patients with a history of heart failure.

Special caution is necessary for patients suffering from or having suffered from recurrent eczema, gastric ulceration or cardiovascular disorders.

Amantadine should be used with caution in patients with hepatic or renal impairment. In case of impaired renal function, the dose should be adjusted accordingly and ideally amantadine plasma concentrations should be monitored. Since only small amounts of amantadine are removed by haemodialysis, the dose should be accurately adjusted in patients with renal failure to avoid undesirable effects (see sections 4.2 and 4.9).

Caution is required in patients with hypotension and cardiac arrhythmias and dopamine-related endocrine disorders.

Since amantadine has anticholinergic effects, Amantadine should not be given to patients with untreated narrow-angle glaucoma.

An increase in hallucinations, confusion and nightmares can occur. In these cases, amantadine should be given with caution. Hallucinations, confusion and nightmares are more common when amantadine is co-administered with anticholinergic agents or when the patient has an underlying psychiatric disorder.

A few cases of Neuroleptic Malignant Syndrome (NMS) have been reported in Parkinson's patients taking amantadine, both during the use and sometime after stopping amantadine. A causal relationship with the use of Amantadine is not clear.

If blurred vision or other vision problems occur, an ophthalmologist should be consulted to rule out corneal oedema. If corneal oedema is diagnosed, amantadine treatment should be discontinued.

Discontinuation of treatment
Treatment with amantadine should not be stopped abruptly. Discontinuation of amantadine treatment may result in deterioration of Parkinson's disease symptoms, symptoms similar to Neuroleptic Malignant Syndrome (NMS) (see also above), catatonia as well as a cognitive manifestation (e.g. confusion, disorientation, deterioration of mental status, delirium).

Impulse control disorders
Patients should be regularly monitored for the development of impulse control disorders. Patients and caregivers should be aware that the behaviour of patients treated with medication with a dopaminergic effect, including Amantadine, may develop symptoms of impulse control disorder, including pathological gambling, increased libido, hypersexuality, compulsive spending or buying behaviour, binge eating and compulsive eating behaviour. A dose reduction or gradual tapering and stopping of treatment should be considered if such symptoms develop.

Excipients
Amantadine contains lactose. Patients 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

Concomitant administration of amantadine and anticholinergics or levodopa may increase confusion, hallucinations, nightmares, gastrointestinal discomfort, or other anticholinergic side effects, such as disturbed accommodation, dry mouth and urinary retention. This should be taken into account with concomitant use.

In isolated cases, psychological decompensation has been reported in patients concomitantly receiving amantadine and antipsychotics or levodopa. Concomitant use is therefore not recommended.

Concomitant administration of amantadine and drugs or substances (e.g. alcohol) acting on the central nervous system may result in additive central nervous system toxicity. Careful monitoring 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 components apparently reduce the clearance of amantadine, leading to higher plasma concentrations and toxic effects (confusion, hallucinations, ataxia, myoclonus). **Concomitant use is therefore not recommended.**

4.6 Fertility, pregnancy and lactation

Pregnancy and women of childbearing potential
There are insufficient data on the use of amantadine during pregnancy. Observations in humans have indicated that the substance could be harmful to pregnancy (including miscarriages, molar pregnancy, heart defects). Studies in animals have shown reproductive toxicity (see section 5.3).
Women of childbearing potential must use effective contraception during treatment and for 5 days after the last dose of amantadine.
Amantadine must not be used during pregnancy unless strictly necessary. Detailed ultrasound monitoring may be considered after exposure during the first trimester.

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 insufficient data on fertility to estimate any potential risk to humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking Amantadine should be cautioned that dizziness, visual disturbances and other central nervous system symptoms (see section 4.8) may occur and that the patient's ability to react may be impaired. Amantadine may therefore affect the ability to drive and use machines.

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 often 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
Undesirable effects reported during clinical trials, post-marketing use and literature are listed according to the MedDRA system/organ classifications. Within each system/organ class, undesirable effects are listed by frequency, the most frequent first, using the following distribution: 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 (frequency cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

Blood and lymphatic system disorders	
Very rare:	Leucopenia.
Metabolism and nutrition disorders	
Common:	Decreased appetite.
Psychiatric disorders:	
Common:	Depression, anxiety, improved mood, agitation, nervousness, insomnia, hallucinations, nightmares, disturbance of attention.
Rare:	Confused state, disorientation, psychotic disorder.
Not known:	Impulse control disorders[1], delirium, hypomania, mania.
Nervous system disorders	
Common:	Dizziness, feeling light-headed, headache, lethargy, ataxia, dysarthria.
Rare:	Tremor, dyskinesia, convulsions.
Very rare:	Symptoms similar to Neuroleptic Malignant Syndrome (NMS) (see section 4.4).
Eye disorders	
Uncommon:	Blurred vision.
Rare:	Corneal lesions, e.g., punctate subepithelial clouding which could be due to superficial punctate keratitis, corneal epithelial oedema, and markedly reduced visual acuity.
Cardiac disorders	
Common:	Palpitations.
Very rare:	Heart failure.
Vascular disorders	
Common:	Orthostatic hypotension.
Gastrointestinal disorders	
Common:	Dry mouth, nausea, vomiting, constipation.
Rare:	Diarrhoea.
Skin and subcutaneous tissue disorders	
Very common:	Livedo reticularis
Common:	Hyperhidrosis.
Rare:	Rash.
Very rare:	Photosensitivity reaction.
Renal and urinary disorders	
Rare:	Urinary retention, urinary incontinence.

General disorders and administration site conditions	
Very common:	Peripheral oedema.
Not known:	Hypothermia.
Investigations	
Very rare:	Reversible increase of liver enzymes.

Additional undesirable effects reported during post-marketing use and literature (frequency of occurrence unknown)
[1] *Impulse control disorders*
Pathological gambling, increased libido, hypersexuality, compulsive spending or buying behaviour, binge eating and compulsive eating behaviour may occur in patients treated with medicines with dopaminergic effects, including Amantadine (see section 4.4).

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 national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

Overdose (acute overdose due to multiple maximum recommended doses or overexposure due to high doses in elderly and/or in patients with renal impairment) with Amantadine may have fatal consequences (see section 4.4).

Symptoms
Neuromuscular disorders and symptoms of acute psychosis are important features of acute amantadine poisoning.

Psychiatric disorders
Confusion, disorientation, delirium, visual hallucinations, aggression/hostility.

Nervous system disorders
Hyperreflexia, motor restlessness, convulsions, extrapyramidal symptoms (torsional spasms, assuming a dystonic posture), myoclonus, reduced level of consciousness and coma.

Eye disorders
Dilated pupils.

Cardiac disorders
Cardiac arrest and sudden cardiac death have been reported. Sinus tachycardia, arrhythmia. Ventricular ectopy, ventricular fibrillation and torsade de pointes have been described.

Vascular disorders
Hypertension.

Respiratory, thoracic and mediastinal disorders
Hyperventilation, pulmonary oedema, breathing difficulties including "adult respiratory distress syndrome".

Gastrointestinal system
Nausea, vomiting, dry mouth, constipation.

Renal and urinary disorders
Urine retention, renal dysfunction, including an increase in BUN and decreased creatinine clearance.

Combined poisoning
The peripheral and central undesirable effects of anticholinergic medicinal products are enhanced by the concomitant use of amantadine. Acute psychotic reactions, which may be identical to those caused by atropine poisoning, may occur if high doses of anticholinergics are used. If alcohol or substances with a stimulating effect on the central nervous system have been taken concomitantly, the symptoms of acute poisoning with amantadine may be worsened or adjusted.

Treatment

There is no specific antidote.

- *Removal and/or inactivation of the substance(s) responsible for the poisoning:* inducting vomiting and/or gastric aspiration or flushing, activated charcoal, salt laxative, if considered appropriate. Since amantadine is largely excreted unchanged in the urine, stimulating the excretory function of the kidney may be effective in removing it from the blood circulation. Making the urine more acidic promotes the excretion of amantadine in the urine. Haemodialysis does not remove significant amounts of amantadine; in patients with renal failure, after taking 300 mg, only 7 to 15 mg was removed during a 4-hour haemodialysis.
- Monitor blood pressure, pulse, ECG, respiration and body temperature, and treat possible hypotension and cardiac arrhythmias, as necessary. Caution is required when administering adrenergic components in cases of cardiac arrhythmias and hypotension, as the clinical status may deteriorate due to the arrhythmogenic property of adrenergic components.
- *Convulsions and excessive motor agitation*: administer anticonvulsants such as diazepam intravenously, paraldehyde intramuscularly or rectally, or phenobarbital intramuscularly.
- *Acute psychotic symptoms, delirium, dystonic posturing, myoclonic manifestations*: physostigmine by slow intravenous infusion (doses of 1 mg adults and 0.5 mg in children) with repeated administration according to initial response and the subsequent need, has been reported.
- *Urinary retention:* bladder should be catheterised; an internal catheter can remain in place for the time required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Adamantane derivatives, dopaminergic agent.
ATC code: N04BB01.

Amantadine is believed to act by enhancing the release of dopamine from central neurons and delaying its reuptake into synaptic vesicles. In addition, it could have some anticholinergic activity.
When administered alone or in combination with other medicinal products, amantadine improves the main signs and symptoms of Parkinson's disease.
The effect generally occurs two to five days after the start of treatment. In particular, it has a positive effect on akinesia, rigidity and tremor. With continued treatment, Amantadine loses its efficacy after a longer or shorter time.

5.2 Pharmacokinetic properties

Absorption
Amantadine is absorbed slowly but almost completely. Maximum plasma levels of approximately 250 ng/ml or 500 ng/ml, respectively, are reached within 3 to 4 hours after a single administration of 100 mg or 200 mg amantadine. After repeated administration of 25, 100 or 150 mg twice daily, steady-state plasma concentrations of 110, 302 or 588 ng/ml, respectively, are reached within 3 days.

Distribution
In vitro, 67% of amantadine is bound to plasma proteins. A substantial part of amantadine is bound to red blood cells. The amantadine concentration in erythrocytes in healthy volunteers is 2.66 times the plasma concentration.
The apparent volume of distribution (V_D) is 5 to 10 l/kg, suggesting strong tissue binding. V_D decreases 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. The average ratio of cerebrospinal fluid (CSF) to serum total amantadine is approximately 0.76.

Biotransformation
Amantadine is metabolised to a minor extent and eight metabolites of amantadine have been identified. The main metabolite, the N-acetyl metabolite, accounts for 5-15% of the administered dose. The pharmacological activity of the metabolites is unknown.

Elimination
Amantadine is eliminated in healthy young adults with a mean plasma elimination half-life of 15 hours (10 to 31 hours).

The elimination half-life of amantadine in brain tissue (6.5 days) is much longer than that in blood.
The total plasma clearance is approximately equal to the renal clearance (250 ml/min). The renal clearance of amantadine is much higher than the creatinine clearance, suggesting renal tubular secretion. The pH of the urine has a major influence on the elimination rate. Increasing the pH of urine can lead to a significant decrease in the elimination rate of amantadine.

Linearity/non-linearity
Amantadine exhibits dose-proportional pharmacokinetics at a dose range of 100 to 200 mg.

Characteristics in special patient populations

Elderly patients
Compared with data from healthy young adults, the half-life is doubled and renal clearance reduced. The ratio of renal clearance to creatinine clearance is lower in the elderly than in the young. In general, tubular secretion is more reduced than the glomerular filtration in the elderly. In elderly patients with renal impairment, repeated administration of 100 mg daily for 14 days resulted in plasma concentrations in the toxic range.

Patients with renal impairment
Since amantadine is mainly excreted by the kidneys, accumulation of amantadine may occur in patients with impaired renal function, leading to serious side effects. A creatinine clearance of less than 40 ml/min [1.73 m^2] causes a three to five times longer half-life and a five times lower total and renal clearance. Renal elimination is dominant even in renal insufficiency. Elderly patients or patients suffering from renal insufficiency should receive an adequately reduced dose. The amantadine plasma concentration to be achieved should not exceed a maximum of 300 ng/ml.

Haemodialysis patients
Haemodialysis removes little amantadine; this ineffectiveness may be related to its strong tissue binding. Less than 5% of a dose is removed during 4 hours of haemodialysis. The average half-life reaches 24 hours of dialysis.

Patients with impaired liver function
The influence of impaired liver function on the pharmacokinetics of amantadine is unknown. Only a small portion of amantadine undergoes hepatic metabolism (see '*Biotransformation*' in section 5.2).

Nutritional effect
Food has no major influence on the pharmacokinetics of amantadine.

Ethnicity
It is unknown whether the pharmacokinetics of amantadine is controlled by genetic factors.

5.3 Preclinical safety data

Amantadine hydrochloride showed a low level of acute toxicity in various animal studies. Sub-chronic oral toxicity studies have been performed in rats, dogs and monkeys. There was no evidence of specific toxicity. Chronic toxicity studies conducted in rats and dogs for up to two years showed no specific toxicity.
In vitro and in vivo studies showed that amantadine is not mutagenic. Carcinogenicity studies have not been conducted. 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 in this study was not sufficient to fully evaluate the carcinogenic potential.
In embryotoxicity studies in rats, mice and rabbits, only embryolethal effects and malformations have been seen in rats. There was an increase in oedema, misplacement of the hind legs, bone abnormalities (missing ribs, aplasia of the caudal vertebra). The lowest dose at which effects occurred in rats was 15 times higher than the maximum human dose. Its relevance to humans is unknown.
Although effects on childbearing potential have not been sufficiently studied, there is evidence of impaired childbearing potential in rats at equal doses where reproductive toxicity was observed.

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

Do not store above 30˚C.

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 and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Renata Pharmaceuticals (Ireland) Limited
13-18 City Quay
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22865/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th February 2022

10 DATE OF REVISION OF THE TEXT

December 2023