

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amantadine Hydrochloride 100mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 100mg amantadine hydrochloride.

Excipient(s) with known effect:

Each hard capsule contains 20mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Brownish-red, size 4, hard gelatin capsules.

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.

Prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus. It is suggested that Amantadine capsules be given to patients suffering from clinical influenza in which complications might be expected to occur. In addition, Amantadine Capsules are recommended prophylactically in cases particularly at risk. This can include those with chronic respiratory disease or debilitating conditions, the elderly and those living in crowded conditions. It can also be used for individuals in families where influenza has already been diagnosed, for control of institutional outbreaks or for those in essential services who are unvaccinated or when vaccination is unavailable or contra-indicated.

Amantadine Capsules do not completely prevent the host immune response to influenza A infection, so individuals who take this drug still develop immune responses to the natural disease or vaccination and may be protected when later exposed to antigenically related viruses. Amantadine Capsules may also be used in 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).

4.2 Posology and method of administration

Posology

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. 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

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.

Infection caused by Influenza A virus

Treatment: It is advisable to start treating influenza as early as possible and to 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 one or two days and the inflammatory reaction of the bronchial tree that usually accompanies influenza resolves more quickly.

Prophylaxis: Treat daily for as long as protection from infection is required. In most instances this is expected to be for 6 weeks. When used with inactivated influenza A vaccine, amantadine is continued for 2 to 3 weeks following inoculation.

Adults: 100mg daily for the recommended period.

Paediatric population with infection caused by Influenza A virus

Children aged 10-15 years: 100mg daily for the recommended period.

Children under 10 years of age: Dosage not established.

Special populations

Elderly patients over 65 years of age with infection caused by Influenza A virus

Plasma amantadine concentrations are influenced by renal function. In elderly patients, the elimination half-life is longer and renal clearance of the compound is diminished in comparison to young people. A daily dose of less than 100mg, or 100mg given at intervals of greater than one day, may be appropriate.

Renal Impairment in Parkinson's disease, herpes zoster and infection caused by Influenza A virus

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	100mg every 2-3 days
>35	100mg daily

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
- 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.

Resistance to amantadine occurs during serial passage of influenza virus strains in vitro or in vivo in the presence of the drug. Apparent transmission of drug-resistant viruses may have been the cause of failure of prophylaxis and treatment in household contacts and in 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.

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, increase 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.

Paediatric population

Hypothermia has been observed in children, especially in those younger than 5 years of age. Caution should be exercised when prescribing Amantadine capsules to children for the prevention and treatment of influenza type A virus (see section 4.2).

Excipient warnings

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, 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 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.

Fertility

No data on the effects of amantadine on human fertility are available.

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. If taken concomitantly with other products affecting the CNS, additive adverse effects could be seen.

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.

The side effects reported after the pivotal clinical studies in influenza in over 1200 patients receiving amantadine at 100mg daily were mostly mild, transient, and equivalent to placebo. Only 7% of subjects reported adverse events, many being similar to the effects of influenza itself. The most commonly reported effects were gastro-intestinal disturbances (anorexia, nausea), CNS effects (loss of concentration, dizziness, agitation, nervousness, depression, insomnia, fatigue, weakness), or myalgia.

The following undesired events, listed by MedDRA system organ class, have been reported. The following definitions of frequencies are used:

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); Not known (cannot be estimated from the available data).

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.

System Organ Class	Frequency	Undesirable effect
Blood and lymphatic system disorders	Very rare	Leucopenia, reversible elevation of liver enzymes
Psychiatric disorders	Not known	Impulse control disorders ⁵
Nervous system disorders	Common	Anxiety, elevation of mood, light-headedness, headache, lethargy, hallucinations, nightmares, ataxia, slurred speech, loss of concentration, nervousness, depression, insomnia, myalgia, hallucinations, confusion and nightmares ¹
	Rare	Confusion, disorientation, psychosis, tremor, dyskinesia, convulsions, neuroleptic malignant-like syndrome
	Not known	Delirium, hypomanic state and mania ²

System Organ Class	Frequency	Undesirable effect
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
	Uncommon	Blurred vision
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
General disorders	Not known	Hypothermia ⁴

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.

⁴ in post-marketing exposure hypothermia has been reported in children mainly those younger than 5 years of age (see section 4.4). The frequency cannot be established.

⁵ 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 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 Yellow Card Scheme at 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 a 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: anti-parkinsonian agent or anti-influenzal virostatic, ATC code: N04B B01

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.

Influenza A Virus: Amantadine specifically inhibits the replication of influenza A viruses at low concentrations. If using a sensitive plaque-reduction assay, human influenza viruses, including H1N1, H2N2 and H3N2 subtypes, are inhibited by $\leq 0.4 \mu\text{g/ml}$ of amantadine. Amantadine inhibits an early stage in viral replication by blocking the proton pump of the M2 protein in the virus. This has two actions; it stops the virus un-coating and inactivates newly synthesised viral haemagglutinin. Effects on late replicative steps have been found for representative avian influenza viruses.

Clinical efficacy and safety

Data from tests with representative strains of influenza A virus indicate that Amantadine capsules is likely to be active against previously unknown strains, and could be used in the early stages of an epidemic, before a vaccine against the strain is generally available.

5.2 Pharmacokinetic properties

Absorption

Amantadine is absorbed slowly but almost completely. Peak plasma concentrations of approximately 250ng/ml and 500ng/ml are attained within 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.

Special 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 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 in 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 100mg/kg proved to be teratogenic. This is 33-fold the recommended dose of 100mg for influenza. The maximum recommended dose of 400mg in Parkinson's disease 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

Capsule filling

Lactose monohydrate

Povidone K-30

Magnesium stearate

Capsule Shell

Gelatine

Red iron oxide (E172)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC aluminium blister

Pack sizes of 14, 28 and 56 capsules

Not all pack sizes may be marketed

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Manx Healthcare Ltd
Taylor Group House
Wedgnoock Lane
Warwick
CV34 5YA

8 MARKETING AUTHORISATION NUMBER(S)

PL 14251/0131

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11/03/2021

10 DATE OF REVISION OF THE TEXT

11/03/2021