SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trilasym 50 mg/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Oral Solution contains 50 mg of amantadine hydrochloride.

Excipient(s) with known effect:

Each 5 ml also contains:

3250 mg of sorbitol (E420)

10 mg of sodium benzoate (E211)

6.5 mg raspberry flavour containing ethanol, propylene glycol (E 1520) and benzyl alcohol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

Clear, colourless, raspberry-flavoured liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus

Trilasym is indicated in patients suffering from clinical influenza in which complications might be expected to occur.

Additionally, amantadine is recommended prophylactically in cases particularly at risk, including:

- those with chronic respiratory disease or debilitating conditions;
- the elderly;
- those living in crowded conditions;
- 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.

Trilasym does 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.

Trilasym is also indicated 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).

Parkinson's disease

Herpes zoster

Trilasym is indicated in elderly or debilitated patients in whom the physician suspects that a severe and painful rash could occur. Trilasym can significantly reduce the proportion of patients experiencing pain of long duration.

4.2 Posology and method of administration

Influenza A

Treatment: When treating influenza, the treatment should start 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 while the protection from infection is required. In most of the cases 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: 10 m l (100 mg) daily for the recommended period.

Children aged 10-15 years: 10 m l (100 mg) daily for the recommended period.

Children under 10 years of age: Dosage not established.

This medicine should not be used in children under the age of 3 years old.

Adults over 65 years of age: A daily dose of less than 10 m l (100 mg), or 10 ml (100 mg) given at intervals of greater than one day, may be appropriate, dependent on the renal function.

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.

Parkinson's disease

Initially 10 ml (100 mg) daily for the first week, increasing to 10 ml (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.

Adults over 65 years of age: 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.

Trilasym 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.

Withdrawal: Trilasym 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

10 ml (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.

Special populations

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	Trilasym contraindicated
15 – 35	10 ml (100 mg) every 2 to 3 days
> 35	10 ml (100 mg) every day

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 listed in section 6.1
- Individuals subject to convulsions
- A history of gastric ulceration
- Severe renal disease
- Pregnancy and breast-feeding

4.4 Special warnings and precautions for use

Trilasym should be used with caution in

- patients with confusional or hallucinatory states or underlying psychiatric disorders
- patients with liver or kidney disorders
- patients suffering from, or who have a history of, cardiovascular disorders.
- when prescribing Trilasym with other medications having an effect on the CNS (see section 4.5).

Abrupt discontinuation

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).

Trilasym 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

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.

Attempted suicide

The smallest quantity consistent with good patient management should be prescribed, as there have been cases of attempted suicide with amantadine

Peripheral oedema/Glaucoma

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 4 weeks) with amantadine. This should be taken into account in patients with congestive heart failure. Trilasym 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.

Paediatric population

This medicine should not be used in children under the age of 3 years old.

Hypothermia- Hypothermia has been observed in children, especially in those younger than 5 years of age. Caution is advised when prescribing amantadine to children for the prevention and treatment of influenza type A virus (see also section 4.2).

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 Trilasym. Dose reduction or tapered discontinuation should be considered if such symptoms develop.

This medicinal product contains Benzyl alcohol, which has been linked with the risk of severe side effects including breathing problems (called “gasping syndrome”) in young children.

4.5 Interaction with other medicinal products and other forms of interaction

Anticholinergic agents or levodopa:

Concurrent administration 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.

Drugs or substances acting on the CNS (e.g. alcohol):

Concomitant use may result in additive CNS toxicity. Close observation is recommended (see section 4.9).

Combination diuretics (hydrochlorothiazide + potassium sparing diuretics):

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. Trilasym is contraindicated during pregnancy and in women trying to become pregnant.

Breastfeeding

Trilasym is excreted in human milk. Undesirable effects have been reported in breast-fed infants. Trilasym should not be used during breast-feeding.

Fertility

There are insufficient data to adequately assess effects on the reproductive system.

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.

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.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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).

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

Organ system	**Frequency**	**Adverse effect**
Blood and lymphatic system disorders	Very rare	leukopenia, hepatic enzyme increased (reversible)
Psychiatric disorders	Not known	Impulse control disorders[5]
Nervous system disorders	Common	anxiety, euphoric mood, dizziness, headache, lethargy, hallucination, nightmare, ataxia, dysarthria, vision blurred, disturbance in attention, nervousness, depression, insomnia, myalgia, confusional state[1]
	Rare	confusion, disorientation, psychotic disorder, tremor, dyskinesia, seizure, neuroleptic malignant syndrome
	Not known	delirium, hypomania and mania[2]
Eye disorders	Uncommon	blurred vision
	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 peripheral, livedo reticularis[3]
	Common	palpitations, orthostatic hypotension
	Very rare	cardiac insufficiency/failure
Gastrointestinal disorders	Common	dry mouth, decreased appetite, nausea, vomiting, constipation
	Rare	diarrhoea
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Rare	rash
	Very rare	photosensitivity reaction
Renal and urinary disorders	Rare	urinary retention, urinary incontinence
General disorders and administration site conditions	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.

 In post-marketing exposure hypothermia has been reported in children mainly those younger than 5 years of age (see also 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 Trilasym (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 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 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: Antiparkinsonian agent and anti-influenzal virostatic.

ATC code: N04B B01

Mechanism of action

Influenza: Trilasym 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 ≤0.4µg/ml of amantadine. Trilasym 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 uncoating and inactivates newly synthesised viral hemagglutinin. Effects on late replicative steps have been found for representative avian influenza viruses. Data from tests with representative strains of influenza A virus indicate that amantadine 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 causative strain is widely available.

Herpes Zoster: The mechanism of action of amantadine in herpes zoster has not been fully characterised.

Parkinson's disease: Trilasym has been shown to be a low affinity antagonist at the N-methyl-D-aspartate (NDMA) subtype of glutamate receptors. Over activity 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 NDMA subtype of glutamate receptors. In addition, amantadine may also exert some anticholinergic activity.

5.2 Pharmacokinetic properties

Absorption: Trilasym 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: Trilasym 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: Trilasym 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 Trilasym 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 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 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. This is 33-fold the recommended dose of 100 mg for influenza. The maximum recommended dose, of 400 mg in Parkinson’s disease, 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

Sodium benzoate (E211)

Sorbitol (E420)

Raspberry flavour - containing ethanol, propylene glycol (E 1520) and benzyl alcohol

Citric acid monohydrate

Purified Water

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

After first opening the bottle: 1 month

6.4 Special precautions for storage

Store below 25°C

Store in the original bottle, in order to protect from light.

6.5 Nature and contents of container

Type III amber glass bottle with a tamper evident polypropylene child-resistant screw cap with a polyethylene inner liner containing 150ml of solution with a polypropylene dosing cup.

Pack size: 150 ml

6.6 Special precautions for disposal

The box containing this medicine contains a plastic measuring cup. The cup is marked in ml (millilitres) to help measuring out the correct amount. This medicine should be taken using the measuring cup and the cup should be rinsed out with water after each use.

7 MARKETING AUTHORISATION HOLDER

Fontus Health Ltd

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Walsall

WS4 2BX

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 42924/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/05/2019

10 DATE OF REVISION OF THE TEXT

16/09/2019