SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lysovir 100mg Capsules

Amantadine hydrochloride 100mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 100mg of Amantadine hydrochloride

Excipients with known effect:
Each capsule contains 20.5mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Reddish-brown, hard gelatin capsules, printed SYMM in white on both the cap and body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis and treatment of signs and symptoms of infection caused by influenza A virus. It is suggested that Lysovir/Amantadine capsules be given to patients suffering from clinical influenza in which complications might be expected to occur. In addition, Lysovir/Amantadine capsules is 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.

Lysovir/Amantadine capsules 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. Lysovir/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

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.

Children over 10 years of age, adolescents and adults: The posology is the same as in adults.

Children under 10 years of age: Dosage not established.

Elderly: 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 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	Lysovir/Amantadine capsules contra-indicated.
15 – 35	100mg every 2 to 3 days.
> 35	100mg 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

Lysovir/Amantadine capsules 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 Lysovir/Amantadine capsules 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

Lysovir/Amantadine capsules 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.

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

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.

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.

Hypothermia

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

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

Special precautions
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. Lysovir/Amantadine capsules is contra-indicated during pregnancy and in women wishing to become pregnant.

Breastfeeding

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

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

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.

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.

Tabulated list of adverse reactions

The following list of adverse reactions is based on clinical trial experience and/or post-marketing 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 Class	Adverse Drug Reactions

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 (see section 4.4), seizure, 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
Renal and urinary disorders	*Rare* urinary retention, urinary incontinence
General disorders and administration site conditions	*Not known* hypothermia* (see section 4.4)
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.

In post-marketing exposure hypothermia has been reported in children mainly those younger than 5 years of age (see also section 4.4 Special warnings and precautions for use).

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 Symmetrel/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 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-influenzal virostatic

ATC code N04B B01

Mechanism of action

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 ≤0.4*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 uncoating and inactivates newly synthesised viral haemagglutinin. 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 Lysovir/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 causative 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.

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 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

Lactose, povidone, magnesium stearate. Capsule shell: gelatin, titanium dioxide (E171), red iron oxide (E172) and monogramming ink S-1-7085 white containing: titanium dioxide (E171), ammonium hydroxide 28%, propylene glycol (E1520), simethicone or SB-0007P white ink containing: shellac, propylene glycol, sodium hydroxide, povidone, titanium dioxide (E171).

6.2 Incompatibilities

None known

6.3 Shelf life

Five years.

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVdC blister packs of 5 or 14 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road
Hampden Park
Eastbourne
BN22 9AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/2250

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/02/2009

10 DATE OF REVISION OF THE TEXT

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