

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Demitens 25 mg/5 ml Oral Solution

Atenolol 25 mg/5 ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 25 mg of atenolol.

Excipients with known effect:

Each 5ml contains:

Maltitol liquid (E965) 1 ml

Sodium methyl parahydroxybenzoate (E219) 9 mg

Sodium propyl parahydroxybenzoate (E217) 1 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution

Clear solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atenolol Oral Solution is indicated in adults for:

- i) Management of hypertension
- ii) Management of angina
- iii) Management of cardiac arrhythmias
- iv) Myocardial infarction. Early intervention in the acute phase.

4.2 Posology and method of administration

Posology

Atenolol oral solution is intended for patients unable to swallow atenolol tablets. The dose must always be adjusted to individual requirements of the patients, with the lowest possible starting dosage. The following are guidelines:

Adults:

Hypertension: Two or four 5 ml spoonfuls daily *i.e.* 50 mg or 100 mg in patients unable to take 50 mg or 100 mg tablets.

Most patients respond to 100 mg (four 5 ml spoonfuls) once daily. Some patients, however, will respond to 50 mg (two 5 ml spoonfuls) given as a single daily dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining atenolol with other antihypertensive agents.

Angina: Most patients with angina pectoris will respond to 100 mg (four 5 ml spoonfuls) given orally once a day, or 50 mg (two 5 ml spoonfuls) given twice daily. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac Arrhythmias: A suitable initial dose of atenolol injection is 2.5 mg (5 ml) injected intravenously over a 2.5 minute period (*i.e.* 1 mg/minute). This may be repeated at 5 minute intervals until a response is observed up to a maximum dosage of 10 mg. If atenolol injection is given by infusion, 0.15 mg/kg body weight may be administered over a 20 minute period. If required, the injection or infusion may be repeated every 12 hours. Having controlled the arrhythmias with intravenous atenolol, a suitable oral maintenance dosage is 50-100 mg (two to four 5 ml spoonfuls of Atenolol Oral Solution) daily, given as a single dose.

Myocardial Infarction: For patients suitable for treatment with intravenous beta-adrenoceptor blockade and presenting within 12 hours of the onset of the chest pain, atenolol injection 5-10 mg should be given by slow intravenous administration (1 mg/minute) followed by Atenolol Oral Solution 50 mg (two 5 ml spoonfuls) orally about 15 minutes later, provided no untoward effects have occurred from the intravenous dose. This should be followed by a further 50 mg orally (two 5 ml spoonfuls), 12 hours after the intravenous dose and then 12 hours later by 100 mg (four 5 ml spoonfuls) orally, to be given once daily. If bradycardia and/or hypotension requiring treatment, or any other untoward effects occur, atenolol should be discontinued.

Special populations

Elderly: Dosage requirements may be reduced, especially in patients with impaired renal function.

Renal impairment: Since atenolol is excreted via the kidneys, dosage should be adjusted in cases of severe impairment of renal function. No significant accumulation of atenolol occurs in patients who have a creatinine clearance greater than 35 ml/min/1.73 m² (normal range is 100-150 ml/min/1.73 m²).

For patients with a creatinine clearance of 15-35 ml/min/1.73 m² (equivalent to serum creatinine of 300-600 micromol/litre) the oral dose should be 50 mg (two 5 ml spoonfuls) daily and the intravenous dose should be 10 mg once every two days.

For patients with a creatinine clearance of <15 ml/min/1.73 m² (equivalent to serum creatinine of >600 micromol/litre) the oral dose should be 25 mg (one 5 ml spoonful) daily or

50 mg (two 5 ml spoonfuls) on alternate days and the intravenous dose should be 10 mg once every four days.

Patients on haemodialysis should be given 50 mg (two 5 ml spoonfuls) orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Paediatric population

There is no paediatric experience with atenolol and for this reason it is not recommended for use in children.

Method of administration

For oral use.

4.3 Contraindications

Atenolol, as with other beta-adrenoceptor blocking active substances, should not be used in patients with any of the following:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- cardiogenic shock
- uncontrolled heart failure
- sick sinus syndrome
- second or third degree heart block
- untreated phaeochromocytoma
- metabolic acidosis
- bradycardia (<45bpm)
- hypotension
- severe peripheral arterial circulatory disturbances.

4.4 Special warnings and precautions for use

Atenolol as with other beta-blockers:

- Should not be withdrawn abruptly. The dosage should be withdrawn gradually over a period of 7-14 days, to facilitate a reduction in beta-blocker dosage. Patients should be followed during withdrawal, especially those with ischaemic heart disease.
- When a patient is scheduled for surgery, and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk-benefit assessment of stopping beta-blockade should be made for each patient. If treatment is continued, an anaesthetic with little negative inotropic activity should be selected to minimise the risk of myocardial depression. The patient may be protected against vagal reactions by intravenous administration of atropine.

- Although contraindicated in uncontrolled heart failure (see Section 4.3), it may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.
- May increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Atenolol is a beta₁-selective beta-blocker; consequently, its use may be considered although utmost caution must be exercised.
- Although contraindicated in severe peripheral arterial circulatory disturbances (see Section 4.3), may also aggravate less severe peripheral arterial circulatory disturbances.
- Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block.
- May mask the symptoms of hypoglycaemia, in particular, tachycardia.
- May mask the signs of thyrotoxicosis.
- Will reduce heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributable to a slow heart rate and the pulse rate drops to less than 50-55 bpm at rest, the dose should be reduced.
- May cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat the allergic reactions.
- May cause a hypersensitivity reaction including angioedema and urticaria.
- Should be used with caution in the elderly, starting with a lesser dose (See Section 4.2).

Since atenolol is excreted via the kidneys, dosage should be reduced in patients with a creatinine clearance of below 35 ml/min/1.73m².

Although cardioselective (beta₁) beta-blockers may have less effect on lung function than non-selective beta-blockers, as with all, beta-blockers, these should be avoided in patients with reversible obstructive airways disease, unless there are compelling clinical reasons for their use. Where such reasons exist, atenolol may be used with caution. Occasionally, some increase in airways resistance may occur in asthmatic patients however, and this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.

The label and patient information leaflet for this product state the following warning: "If you have ever had asthma or wheezing, do not take this medicine without first checking with your doctor."

As with other beta-blockers, in patients with a phaeochromocytoma, an alpha-blocker should be given concomitantly.

Atenolol Oral Solution contains sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217). These may cause allergic reactions (possibly delayed).

This product also contains Maltitol Liquid. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 63.7 mg sodium per 20 ml, equivalent to 3.2% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Combined use of beta-blockers and calcium channel blockers with negative inotropic effects *e.g.* verapamil and diltiazem can lead to an exaggeration of these effects particularly in patients with impaired ventricular function and/or sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines *e.g.* nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency.

Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicinal products are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped. (See also prescribing information for clonidine).

Class I anti-arrhythmic drugs (*e.g.* disopyramide, quinidine) and amiodarone may have a potentiating effect on atrial conduction time and induce negative inotropic effect.

Concomitant use of sympathomimetic agents, *e.g.* adrenaline (epinephrine), may counteract the effect of beta-blockers.

Concomitant use with insulin and oral antidiabetic medicinal products may lead to the intensification of the blood sugar lowering effects of these medicinal products. Symptoms of hypoglycaemia, particularly tachycardia, may be masked (See Section 4.4).

Concomitant use of prostaglandin synthetase inhibiting medicinal products, *e.g.* ibuprofen and indometacin, may decrease the hypotensive effects of beta-blockers.

Caution must be exercised when using anaesthetic agents with atenolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic medicinal products may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

4.6 Fertility, pregnancy and lactation

Caution should be exercised when atenolol is administered during pregnancy or to a woman who is breastfeeding.

Pregnancy

Atenolol crosses the placental barrier and appears in cord blood. No studies have been performed on the use of atenolol in the first trimester and the possibility of foetal injury cannot be excluded. Atenolol has been used under close supervision for the treatment of hypertension in the third trimester. Administration of atenolol to pregnant women in the management of mild to moderate hypertension has been associated with intra-uterine growth retardation.

The use of atenolol in women who are, or may become pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters, since beta-blockers, in general, have been associated with a decrease in placental perfusion which may result in intra-uterine deaths, abortion, immature and premature deliveries.

Breastfeeding

There is significant accumulation of atenolol in breast milk.

Neonates born to mothers who are receiving atenolol at parturition or breastfeeding may be at risk of hypoglycaemia and bradycardia.

Fertility

There is no fertility data available.

4.7 Effects on ability to drive and use machines

Atenolol has negligible influence on the ability to drive and use machines. However, it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

Atenolol is well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of Atenolol.

The following undesired events, listed by body system, have been reported with the following frequencies: 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).

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Thrombocytopenia
Psychiatric disorders	Uncommon	Sleep disturbances of the type noted with other beta-blockers
	Rare	Mood changes, nightmares, confusion, psychoses and hallucinations
	Not known	Depression
Nervous system disorders	Rare	Dizziness, headache and paraesthesia
Eye disorders	Rare	Dry eyes, visual disturbances
Cardiac disorders	Common	Bradycardia
	Rare	Heart failure deterioration, atrioventricular block
Vascular disorders	Common	Peripheral coldness
	Rare	Orthostatic hypotension which may be associated with syncope, intermittent claudication may be increased if already present, in susceptible patients Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints
Gastrointestinal disorders	Common	Gastrointestinal disturbances
	Rare	Dry mouth

Hepatobiliary disorders	Rare	Hepatic toxicity including intrahepatic cholestasis
Skin and subcutaneous tissue disorders	Rare	Alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes, purpura
	Not known	Hypersensitivity reactions, including angioedema and urticaria
Musculoskeletal and connective tissue disorders	Not known	Lupus-like syndrome
Reproductive system and breast disorders	Rare	Impotence
General disorders and administration site conditions	Common	Fatigue
Investigations	Uncommon	Transaminases increased
	Very rare	An increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear

Discontinuance of the medicinal product should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions.

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

The symptoms of overdose may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include: close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any medicinal product still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock. The use of haemodialysis or haemoperfusion may be considered.

Excessive bradycardia can be countered with atropine 1-2 mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10 mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given. Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-blocker blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by bronchodilators.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, ATC Code: C07A B03

Mechanism of action

Atenolol is a beta-blocker which is beta₁-selective, (i.e. acts preferentially on beta₁-adrenergic receptors in the heart). Selectivity decreases with increasing dose.

Atenolol is without intrinsic sympathomimetic and membrane stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure).

As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear.

It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

It is unlikely that any additional ancillary properties possessed by S (-) atenolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Clinical efficacy and safety

Atenolol is effective and well-tolerated in most ethnic populations although the response may be less in black patients.

Atenolol is effective for at least 24 hours after once daily dosing with 10 ml or 20 ml Atenolol Oral Solution. Atenolol Oral Solution facilitates compliance by its acceptability to patients and the once daily dosing regimen. The narrow dose range and early patient response ensure that the effect of the active substance in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginals (see Section 4.5). Since it acts preferentially on beta-adrenergic receptors in the heart, Atenolol may, with care, be used successfully in the treatment of patients with respiratory disease, who cannot tolerate non-selective beta-blockers.

Early intervention with Atenolol in acute myocardial infarction reduces infarct size and decreases morbidity and mortality. Fewer patients with a threatened infarction progress to frank infarction; the incidence of ventricular arrhythmias is decreased and marked pain relief may result in reduced need of opiate analgesics. Early mortality is decreased. Atenolol is an additional treatment to standard coronary care.

5.2 Pharmacokinetic properties

Absorption

Absorption of atenolol following oral dosing is consistent but incomplete (approximately 40-50%) with peak plasma concentrations occurring 2-4 hours after dosing. The atenolol blood levels are consistent and subject to little variability. There is no significant hepatic metabolism of atenolol and more than 90% of that absorbed reaches the systemic circulation unaltered.

Distribution

Atenolol penetrates tissues poorly due to its low lipid solubility and its concentration in brain tissue is low. Plasma protein binding is low (approximately 3%).

Elimination

The plasma half-life is about 6 hours but this may rise in severe renal impairment since the kidney is the major route of elimination.

5.3 Preclinical safety data

Atenolol is an active substance on which extensive clinical experience has been obtained. Relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltitol liquid (E965)

Saccharin sodium (E954)

Citric acid monohydrate

Sodium citrate

Sodium methyl parahydroxybenzoate (E219)

Sodium propyl parahydroxybenzoate (E217)

Orange flavour (contains propylene glycol, E1520)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in the original container.

Discard after 3 months of first opening.

6.5 Nature and contents of container

Amber Type III Glass

Child Resistant Tamper Evident Cap- High density polypropylene cap with a polyethylene lining

Pack sizes available: 300ml

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited

3&4 Quidhampton Business Units

Polhampton Lane

Overton, Hampshire

RG25 3ED

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0526

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/11/2024

10 DATE OF REVISION OF THE TEXT

22/11/2024