SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tapiflex 25 mg/5 ml Oral Solution

Atenolol 25 mg/5 ml Sugar Free Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 25 mg atenolol.

Excipient(s) with known effect
Each 5 ml of this medicine contains 1330 mg sorbitol, 250 mg propylene glycol, 7 mg methyl hydroxybenzoate, 0.7 mg propyl hydroxybenzoate, 2.25 mg ethanol and 8.2 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.

Clear colourless liquid with an odour of lemon and lime.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Atenolol oral solution is indicated for:

- Management of hypertension
- Management of angina
- Management of cardiac arrhythmias
- Myocardial infarction. Early intervention in the acute phase.

4.2 Posology and method of administration

For oral administration.

Atenolol oral solution is intended for patients who are unable to swallow atenolol tablets.

The dose must always be adjusted to individual patient requirements with the lowest possible starting dosage. The following are guidelines.

Adults

Hypertension

50 mg (two 5 ml spoonfuls) or 100 mg (four 5 ml spoonfuls) 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 or 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 a day. It is unlikely that additional benefit will be gained by increasing the dose.

Cardiac arrhythmias

Following the initial control of the arrhythmia with atenolol injection administered by intravenous injection or infusion, a suitable oral maintenance dosage is 50 mg (two 5 ml spoonfuls) to 100 mg (four 5 ml spoonfuls) administered daily as a single dose.

Myocardial infarction

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

Elderly

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

Children

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

Renal failure

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 m^2 (normal range is 100 – 150 ml/min/1.73 m^2).

For patients with a creatinine clearance of 15-35 ml/min/1.73 m^2 (equivalent to serum creatinine of 300 – 600 micromol/litre) the oral dose should be 50 mg (two 5 ml spoonfuls) daily.

For patients with a creatinine clearance of <15 ml/min/1.73 m^2 (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.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Atenolol, as with other beta-blockers, should not be used in patients with any of the following:

- cardiogenic shock
- uncontrolled heart failure
- sick sinus syndrome
- second or third degree heart block
- untreated phaeochromocytoma
- metabolic acidosis
- bradycardia (<45 bpm)
- 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 $beta_1$- 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), it 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 the heart rate, as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms which may be attributed 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 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/1.73 m^2.

Although cardioselective ($beta_1$) 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, this may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline. The label and patient information leaflet for the product state the following warning: “If you have ever had asthma or wheezing, you should not take this medicine unless you have discussed these symptoms with the prescribing doctor”.

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

Excipients:

This medicine contains 5.32 g sorbitol in each 20 ml (four 5 ml spoonfuls) which is equivalent to 266 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicine contains 1 g propylene glycol in each 20 ml (four 5 ml spoonfuls) which is equivalent to 50 mg/ml.

This medicine contains methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reaction (possibly delayed).

This medicine contains 32.8 mg sodium in each 20 ml (four 5 ml spoonfuls) solution, equivalent to 1.64% of the WHO recommended maximum daily intake of 2 g sodium for an adult

This medicine contains small amounts of ethanol (alcohol), less than 100 mg per dose.

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 atrio-ventricular conduction time.

Beta-blockers may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. If the two drugs 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).

Caution must be exercised when prescribing a beta-blocker with Class 1 antiarrhythmic agents such as disopyramide and quinidine.

Concomitant use of sympathomimetic agents, e.g. adrenaline, may counteract the effects of beta-blockers.

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

Concomitant use of prostaglandin synthetase inhibiting drugs (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 drugs 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

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, immature and premature deliveries.

There is significant accumulation of atenolol in breast milk.

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

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

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 adverse events reported are usually attributable to the pharmacological actions of atenolol.

The following adverse events, listed by body system, have been reported. The following convention is used for frequencies: 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) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	
Rare	Thrombocytopenia
Psychiatric disorders	
Uncommon	Sleep disorders of the type noted with other beta-blockers
Rare	Mood altered, nightmares, confusional state, psychotic disorder, hallucination
Not known	Depression
Nervous system disorders	
Rare	Dizziness, headache, paraesthesia
Eye disorders	
Rare	Dry eye, visual impairment
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 disorder

Rare	Dry mouth
Hepato-biliary disorders	
Rare	Hepatotoxicity including cholestasis
Skin and subcutaneous tissue disorders	
Rare	Alopecia, psoriasiform skin reactions, psoriasis, rash, purpura
Not known	Hypersensitivity, including angioedema and urticaria
Musculoskeletal and connective tissue disorders	
Not Known	Lupus-like syndrome
Reproductive system and breast disorders	
Rare	Erectile dysfuction
General disorders and administration site conditions	
Common	Fatigue
Investigations	
Uncommon	Transaminases increased
Very rare	Antinuclear antibody has been observed, however, the clinical relevance of this is not clear

Discontinuance of the drug 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 overdosage 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 drug 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, plain, selective.

ATC code: C07 AB03

Atenolol is a beta-blocker, which is $beta_1$-selective (i.e. acts preferentially on $beta_1$-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.

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

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 drug in individual patients is quickly demonstrated. Atenolol is compatible with diuretics, other hypotensive agents and antianginal agents (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

Following oral dosing atenolol absorption is consistent but incomplete with 40-50% of a dose being absorbed. Peak plasma concentrations occur 2-4 hours after administration. 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. 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. 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%).

5.3 Preclinical safety data

Extensive clinical experience with atenolol has been obtained. Relevant information for the prescriber is provided in sections 5.1 and 5.2.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol 70% solution (E 420)

Propylene glycol (E 1520)

Saccharin sodium

Methyl hydroxybenzoate (E 218)

Propyl hydroxybenzoate (E 216)

Citric acid monohydrate

Trisodium citrate dihydrate

Lemon and lime flavour (containing ethanol)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

Use within one month of first opening.

6.4 Special precautions for storage

Do not store above 25ºC.

Store in the original container.

6.5 Nature and contents of container

Type III amber glass bottle with child resistant and tamper evident polypropylene faced cap with expanded polyethylene liner. Pack size: 300 ml.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Chemidex Pharma Limited

Trading as Chemidex Generics and / or Essential Generics

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8 MARKETING AUTHORISATION NUMBER(S)

PL 17736 / 0068

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/03/2009
19/03/2014

10 DATE OF REVISION OF THE TEXT

24/06/2021