

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trasidrex Tablets.
Cyclopentiazide 0.25mg and Oxprenolol Hydrochloride 160mg
Tablets

2. Qualitative and Quantitative Composition

Oxprenolol hydrochloride Ph.Eur 160 mg
Cyclopentiazide BP 0.25 mg

For excipients, see 6.1

3. Pharmaceutical Form

Coated Tablet

Clinical Particulars

4.1. Therapeutic Indications

In the treatment of hypertension

4.2. Posology and Method of Administration

The dosage should be individualised. The sustained release tablets should be swallowed whole with liquid. When discontinuing prolonged treatment with a β -blocker, the medication should not be stopped abruptly, but withdrawn gradually. The physician may wish to switch to products containing the individual components of Trasidrex, i.e. conventional oxprenolol and cyclopentiazide tablets to facilitate a stepwise reduction in dose.

Adults

In mild to moderate hypertension the recommended dosage is 1 tablet daily in the morning.

Depending on the response it may be necessary to raise the dosage to two tablets daily. This should be done after an interval of about 1 week, because the antihypertensive effect often only sets in slowly after 1-2 weeks. In resistant cases, treatment in combination with other antihypertensives can be given, e.g. with a peripheral vasodilator, calcium channel blocker, or ACE inhibitor (see "Interactions with other medicaments and other forms of interaction").

Children

Adequate experience of the use of Trasidrex in children has not been acquired.

Elderly

No special dosage regime is necessary but concurrent hepatic insufficiency and susceptibility to electrolyte imbalances should be taken into account. The lowest effective dosage should be used.

4.3. Contra-indications

Hypersensitivity to oxprenolol, cyclopentiazide and related derivatives or to any of the excipients, or cross sensitivity to other β -blockers.

Oxprenolol

- Cardiogenic shock.
- Heart failure refractory to treatment.
- Atrioventricular block of second or third degree.
- Sick sinus syndrome.
- Bradycardia (< 45-50 beats/min)
- Hypotension.
- Severe peripheral arterial circulatory disturbances.
- Bronchial asthma and history of bronchospasm. (A warning stating "Do not take this medicine if you have a history of wheezing or asthma" will appear on the label).
- Prinzmetal's angina (variant angina pectoris).
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Use of anaesthetics with a negative inotropic effect.

Cyclopentiazide

- Anuria.
- Renal failure.
- Hepatic failure.
- Refractory hyponatraemia and hypercalcaemia.
- Refractory hypokalaemia and conditions involving increased potassium loss, e.g. salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function.
- Untreated Addison's disease.
- Symptomatic hyperuricaemia (history of gout or uric acid calculi).
- Concomitant treatment with Lithium.
- Hypertension during pregnancy.

4.4. Special Warnings and Precautions for Use

Warnings:

Trasidrex should be used with caution in patients with renal disease or with impaired hepatic function (see "Contraindications" and "Precautions").

Precautions:

Oxprenolol

Owing to the danger of cardiac arrest, a calcium antagonist of the verapamil type must not be administered intravenously to a patient already receiving treatment with a β -blocker (see "Interactions with other medicaments and other forms of interaction").

Owing to the risk of bronchoconstriction, non-selective β -blockers such as oxprenolol should be used with caution in patients with chronic bronchitis or emphysema.

Due to the negative effect on AV conduction time, β -blockers should only be given with caution to patients with AV block of first degree (see "Contraindications").

β -blockers should not be used in patients with untreated congestive heart failure (see "Contraindications"). This condition should first be stabilised.

If the patient develops increasing bradycardia (< 50 - 55 beats/min at rest) and experiences related symptoms, the dosage should be reduced or gradually withdrawn (see "Contraindications").

β -blockers may mask certain clinical signs of hyperthyroidism (e.g. tachycardia), and the patients should be carefully monitored.

β -blockers may reduce liver function and thus affect the metabolism of other drugs. Like many β -blockers, oxprenolol undergoes substantial first-pass hepatic metabolism. In the presence of liver cirrhosis the bioavailability of oxprenolol may be increased leading to higher plasma concentrations (see "Pharmacokinetic properties").

In patients with peripheral circulatory disorders (e.g. Raynaud's disease or syndrome, intermittent claudication), β -blockers should be used with great caution as aggravation of these disorders may occur (see "Contraindications").

In patients with phaeochromocytoma a β -blocker should only be given with an α -blocker, (see "Contraindications").

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking β -blockers, require higher than normal doses of adrenaline. Whenever possible, β -blockers should be avoided (replaced by other antihypertensive drugs) in patients who are at increased risk for anaphylaxis.

In patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dosage should be gradually reduced, i.e. over 1-3 weeks, if necessary at the same time initiating alternative therapy, to prevent exacerbation of angina pectoris.

If a patient receiving oxprenolol requires anaesthesia, the anaesthetist should be informed of the use of the medication prior to the use of a general anaesthetic to permit him to take the necessary precautions. The anaesthetic selected should be one exhibiting as little negative inotropic activity as possible, e.g. halothane/nitrous oxide. If, on the other hand, inhibition of sympathetic tone during the operation is regarded as undesirable, the β -blocker should be withdrawn gradually at least 48 hours prior to surgery.

The full development of the "oculomucotaneous syndrome" as previously described with practolol, has not been reported with oxprenolol. However, some features of this syndrome have been noted such as dry eyes alone or occasionally associated with skin rash. In most cases the symptoms have cleared after withdrawal of treatment. Discontinuation of oxprenolol should be considered and a switch to another antihypertensive drug might be advisable.

Cyclopenthiiazide

Electrolytes

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte unbalance, namely dose dependent hyponatraemia, hypochloremic alkalosis and hypokalaemia. Since the excretion of electrolytes is increased during thiazide treatment, an excessively strict low-salt diet should be avoided.

Periodic serum electrolyte determinations should be carried out, especially in digitalised patients, in the elderly, especially in those suffering from chronic diseases, in patients with liver cirrhosis, who are more susceptible to regulatory disorders affecting the electrolytes and fluid balance, and in patients with oedema due to nephrotic syndrome.

Serum potassium concentrations should be checked initially and 3-4 weeks after the start of therapy. Unless the potassium balance is disturbed by other factors (e.g. vomiting, diarrhoea, change in renal function, malnutrition, liver cirrhosis, hyperaldosteronism, treatment with ACTH or corticosteroids) controls should be carried out every 4-6 months.

Hypokalaemia may be avoided or treated by the use of potassium supplements and/or foods with a high potassium content.

Oral potassium supplementation (e.g. KCl) may be considered in patients receiving digitalis and diuretics, particularly if their plasma potassium concentrations are < 3.0 mmol/L. If oral potassium supplementation is not well tolerated, Trasidrex may be combined with a potassium sparing diuretic e.g. amiloride.

Combined treatment consisting of Trasidrex and a potassium salt or a potassium-sparing diuretic must be avoided in patients also receiving ACE inhibitors.

If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG changes), Trasidrex should be discontinued.

During treatment with thiazides, hyponatraemia accompanied by neurological symptoms (nausea, asthenia, progressive disorientation, apathy) has been observed in isolated cases.

Patients receiving relatively high doses of thiazides may develop hypomagnesaemia accompanied by signs and symptoms such as irritability, muscle cramps, and cardiac arrhythmias.

Metabolic effects

Like other diuretics, thiazides may raise serum uric acid levels, but attacks of gout are rarely observed during chronic treatment.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is not clear.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland associated with hypercalcaemia and hypophosphataemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcaemia occurs, further diagnostic clarification is necessary. The usual complications of hyperparathyroidism, e.g. renal lithiasis, bone resorption, and peptic ulceration, have not been observed.

Others

Lupus erythematosus may become activated under treatment with thiazides.

Oxprenolol and cyclopentiazide

Diabetes/glucose tolerance

β -blockers as well as thiazide diuretics are liable to affect carbohydrate metabolism. Diabetic patients, especially those dependent on insulin, should be warned that β -blockers can mask the signs of hypoglycaemia (e.g. tachycardia) (see "Interactions with other medicaments and other forms of interaction"). Hypoglycaemia, producing loss of consciousness in some cases, may occur in non-diabetic individuals who are taking β -blockers, particularly those who undergo prolonged fasting or strenuous exercise.

Although glucose tolerance may be adversely affected, diabetes mellitus very seldom occurs under treatment.

The concurrent use of β -blockers, thiazide diuretics and antidiabetic medication should always be monitored to confirm that glycaemic control is

well maintained (see "Interactions with other medicaments and other forms of interaction").

Renal function

In patients with renal impairment, the elimination half-life for unchanged oxprenolol is not expected to be significantly different from the subjects with normal renal function, but thiazides accumulate and uraemia may become more marked.

Creatinine clearance, urea and electrolytes should be monitored in patients with renal impairment since they might be more susceptible to the effects of antihypertensive drugs. At creatinine clearance levels of < 30 mL/min (or at serum creatinine levels of greater than 2.5 mg/100 mL = 221 micromol/L), thiazides no longer exert an adequate diuretic effect.

The antihypertensive effect of ACE inhibitors is potentiated by diuretics that increase plasma renin activity. A cautious dosage schedule should therefore be adopted when an ACE inhibitor is added to a diuretic agent.

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

4.5. Interactions with other Medicaments and other forms of Interaction

The antihypertensive effect of Trasidrex is enhanced by concomitant treatment with other antihypertensives.

In addition, the following interactions may occur with the individual components.

Oxprenolol and cyclopentiazide

Antidiabetics

Trasidrex may modify blood glucose concentrations in patients being treated with insulin and oral antidiabetic drugs, and may alter the response to hypoglycaemia by prolonging the recovery (blood glucose rise) from hypoglycaemia, reversing hypotension, and blocking tachycardia. In diabetic patients receiving Trasidrex hypoglycaemic episodes may not result in the expected tachycardia, but hypoglycaemia-induced sweating will occur, and may even be intensified and prolonged (see "Special warnings and special precautions for use").

Hyperglycaemia may also occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during Trasidrex therapy.

During concurrent therapy with antidiabetics a close watch should therefore be kept on carbohydrate metabolism, and the dosage of hypoglycaemic

medication may have to be readjusted (see "Special warnings and special precautions for use").

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs such as indomethacin can reduce the hypotensive effect of Trasidrex and there have been isolated reports of a deterioration in renal function in predisposed patients.

Calcium channel blockers

Calcium channel blockers such as verapamil and diltiazem may potentiate bradycardia, myocardial depression, and hypotension induced by Trasidrex, particularly after intravenous administration of verapamil, the possibility of hypotension cardiac arrhythmia and cardiac arrest cannot be excluded (see "Special warnings and special precautions for use").

Catecholamine-depleting drugs

Catecholamine-depleting drugs, such as guanethidine or monoamine oxydase inhibitors may have an additive effect when administered concomitantly with β -blockers such as oxprenolol and with thiazide diuretics. Patients should be closely observed for hypotension.

Digitalis glycosides

β -blockers and digitalis glycosides may be additive in their depressant effect on myocardial conduction, particularly at the atrioventricular node, resulting in bradycardia or heart block.

Thiazide induced hypokalaemia or hypomagnesaemia may also favour the onset of digitalis-induced cardiac arrhythmias (see "Special warnings and special precautions for use").

Oxprenolol

Alcohol and β -blocker effects on the central nervous system have been observed to be additive and it is possible that symptoms such as dizziness may be exaggerated if alcohol and Trasidrex are taken together (see also "Effects on ability to drive and use machines").

Class I anti-arrhythmic drugs and amiodarone

Drugs such as disopyramide, quinidine and amiodarone may have a potentiating effect on atrial conduction time and induce negative isotropic effect when administered concomitantly with β -blockers.

Sympathomimetic drugs

Non-cardioselective β -blockers such as oxprenolol may enhance the pressor response to sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, and phenylephrine (e.g. local anaesthetics in dentistry, nasal and ocular drops), resulting in hypertension and bradycardia.

Clonidine

When clonidine is used in conjunction with a non-selective β -blocker, such as oxprenolol, treatment with clonidine should be continued for some time after the β -blocker has been discontinued to reduce the danger of rebound hypertension.

Cimetidine

Hepatic metabolism of β -blockers may be reduced by cimetidine, resulting in increased plasma concentrations and prolonged serum half-life. Marked bradycardia may occur.

Ergot alkaloids

Concomitant administration with β -blockers may enhance the vasoconstrictive action of ergot alkaloids.

Anaesthetic agents

β -blockers and certain inhaled anaesthetics may be additive in their cardiodepressant effect. However, continued use of β -blockers during anaesthesia reduces the risk of cardiac arrhythmias and hypertension (see "Special warnings and special precautions for use").

Lignocaine

Concomitant administration with β -blockers may increase blood lidocaine concentrations and potential toxicity; patients should be closely monitored for increased lidocaine effects.

Cyclopentiazide

Lithium

Diuretics raise the blood level of lithium. Where lithium has produced polyuria, diuretics may exert a paradoxical antidiuretic effect, (see Contraindications).

Curare derivatives and antihypertensive drugs

Thiazides potentiate the action of curare derivatives and antihypertensive drugs (e.g. methyl dopa, β -blockers, vasodilators, ACE inhibitors).

Potassium lowering drugs (such as corticosteroids, ACTH, amphotericin B, carbenoxolone)

These drugs may increase the hypokalaemic effect of thiazides.

Allopurinol

Co-administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine

Co-administration of thiazide diuretics may increase the risk of adverse effects caused by amantadine.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate)

Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

Anticholinergics (e.g. atropine, biperiden)

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently owing to a decrease in gastrointestinal motility and stomach-emptying rate.

Cholestyramine

Absorption of thiazide diuretics is decreased by cholestyramine. A decrease in the pharmacological effect of thiazides may be expected.

Vitamin D

Thiazide diuretics may reduce urinary calcium excretion caused by vitamin D, while vitamin D may potentiate the increase in serum calcium caused by thiazides.

Cyclosporin

Concomitant use of thiazide-type diuretics and cyclosporin may increase the risk of hyperuricemia and gout-type complications.

Calcium salts

Concomitant use of thiazide-type diuretics and calcium salts may cause hypercalcaemia by increasing tubular calcium reabsorption.

Diazoxide

Thiazide diuretics may enhance the hyperglycaemic effect of diazoxide.

Methyldopa

There have been reports in the literature of haemolytic anaemia occurring when a thiazide diuretic and methyldopa were administered concomitantly.

Alcohol, barbiturates or narcotics: may potentiate orthostatic hypotension induced by cyclopenthiiazide.

4.6. Pregnancy and Lactation

Trasidrex should not be given during pregnancy unless there are no safer alternatives. If used, as in the case of any form of drug therapy, Trasidrex should be employed with caution, especially in the first 3 months.

β -blockers may reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. Use the lowest possible dose. If possible, discontinue β -blocker therapy at least 2-3 days prior to delivery to avoid the effects of uterine contractility and possible adverse effects, especially bradycardia and hypoglycaemia, in the foetus and neonate.

Cyclopentiazide must not be used to treat hypertension during pregnancy (see "Contraindications"). There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics. Other adverse reactions associated with use in adults may also occur.

Oxprenolol and cyclopentiazide pass into breast milk (see "Pharmacokinetic properties") and although the estimated daily infant dose derived from breast feeding is likely to be very low, breast feeding is not recommended.

Trasidrex may also suppress lactation.

4.7. Effects on Ability to Drive and Use Machines

Patients receiving Trasidrex should be warned that dizziness, fatigue or visual disturbances (see "Undesirable effects") may occur, in which case they should not drive, operate machinery, or do anything else requiring alertness, particularly if they also consume alcohol.

4.8. Undesirable Effects

Frequency estimate: very common >10%, common 1% to < 10%, uncommon 0.1% to < 1%, rare 0.01% to < 0.1%, very rare < 0.01%.

Central nervous system

Common: fatigue, dizziness, headache, mental depression, sleep disturbances, nightmares.

Rare: hallucinations, exertional tiredness.

Uncommon: paresthesias.

Cardiovascular system

Common: postural hypotension which can be aggravated by alcohol, anaesthetics or sedatives, heart failure, peripheral vascular disorders (peripheral coldness).

Uncommon: bradycardia, disturbances of cardiac conduction.

Rare: Raynaud-like symptoms, cardiac arrhythmia.

Gastrointestinal tract

Very common: dry mouth, constipation.

Common: nausea, vomiting, flatulence, loss of appetite.

Uncommon: diarrhoea.

Very rare: pancreatitis, abdominal distress.

Skin and appendages

Common: allergic skin rash, urticaria.

Rare: worsening of psoriasis, photosensitivity.

Very rare: necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus like-lesions, and reactivation of cutaneous lupus erythematosus.

Respiratory system

Common: dyspnoea, bronchospasm.

Sense Organs

Uncommon: visual disturbances.

Very Rare: dry eyes, keratoconjunctivitis.

Blood

Very rare: thrombocytopenia sometimes with purpura, leucopenia, agranulocytosis, bone marrow depression and haemolytic anaemia.

Liver

Rare: intrahepatic cholestasis or jaundice.

Electrolytes and metabolic disorders

Very common: mainly with higher doses, hypokalaemia and rise in serum lipids.

Common: hyponatraemia, hypomagnesaemia, and hyperuricaemia.

Rare: hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic status.

Very rare: hypochloraemic alkalosis.

Other effects:

Common: disturbances of libido and potency.

Very rare: hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary oedema.

4.9. Overdose

Signs and symptoms

Oxprenolol

Poisoning due to an overdose of a β -blocker may lead to pronounced hypotension, bradycardia, conduction abnormalities (first or second degree block, complete heart block, asystole), or even cardiac arrest; heart failure, cardiogenic shock, hypoglycaemia, in addition, dyspnoea, bronchospasm, vomiting, impairment of consciousness, and also generalised convulsions may occur.

The manifestations of poisoning with β -blockers are dependent on the pharmacological properties of the ingested drug. Although the onset of action is rapid, effects of massive overdose may persist for several days despite declining plasma levels. Watch carefully for cardiovascular or respiratory

deterioration in an intensive care setting, particularly in the early hours. Observe mild overdose cases for at least 4 hours for the development of signs of poisoning.

Cyclopentiazide

Additional symptoms due to overdose with cyclopentiazide are nausea, dizziness, somnolence, hypovolaemia, electrolyte disturbances associated with cardiac arrhythmias and muscles spasms.

Treatment

Patients who are seen soon after potentially life-threatening overdose (within 4 hours) should be treated by gastric lavage and activated charcoal.

Treatment of symptoms is based on modern methods of intensive care, with continuous monitoring of cardiac function, blood gases, electrolytes, and if necessary intravenous fluid and electrolytes replacement, and emergency measures such as artificial respiration, resuscitation or cardiac pacemaker.

Significant bradycardia should be treated initially with atropine. Large doses of isoprenaline may be necessary for control of heart rate and hypotension. Glucagon has positive chronotropic and inotropic effects on the heart that are independent of interactions with β -adrenergic receptors, and it represents a useful alternative treatment for hypotension and heart failure.

For the treatment of seizures, diazepam has been effective and is the drug of choice.

For the treatment of bronchospasm, β_2 -agonists (such as salbutamol or terbutaline) or aminophylline are effective bronchodilator drugs. Monitor the patient for dysrhythmias during and after administration.

Patients who recover should be observed for signs of β -blocker withdrawal phenomenon (see "Special warnings and special precautions for use").

Pharmacological Properties

5.1. Pharmacodynamic Properties

Mode of action: Trasidrex contains two components which have different sites of action and whose antihypertensive effects are mutually complimentary.

Oxprenolol

Mechanism of action

Oxprenolol, one of the active substances of Trasidrex, is a non-selective, lipophilic β -blocker exerting a sympatholytic effect and displaying mild to

moderate partial agonist activity (PAA), also known as intrinsic sympathomimetic activity (ISA).

The exact way in which β -blockers exert their antihypertensive action is still not fully understood. Various modes of action have been postulated. In the long run the antihypertensive effect of β -blockers always parallels a decline in peripheral vascular resistance.

Oxprenolol is effective in lowering elevated supine, standing and exertional blood pressure; substantial hypotensive reactions are less likely to occur.

Emotional stress and anxiety states which are largely caused by increased sympathetic drive are alleviated by the sympatholytic effect of oxprenolol.

Cyclopentiazide

Cyclopentiazide, one of the two active substances of Trasidrex, is a benzothiadiazine (thiazide) diuretic.

Thiazide diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting NaCl reabsorption (by antagonising the Na⁺-Cl⁻ co-transporter), and promoting Ca⁺⁺ reabsorption (by an unknown mechanism). Increased delivery of Na⁺ and water to the cortical collecting tubule and/or the higher flow rate lead to more secretion and excretion of K⁺ and H⁺.

In healthy volunteers or in patients with oedema, diuresis is already enhanced after administration of a single dose of 0.125 mg of cyclopentiazide. The resulting increase in urinary excretion of sodium and chloride and the less marked increase in kaliuresis are dose dependent. The diuretic/natriuretic effect appears within 1-3 hours after oral administration of cyclopentiazide, reaches its maximum after 6-9 hours, and subsides within 24 hours.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may become activated. The hypotensive effect is maintained during continued administration, probably owing to a fall in total peripheral vascular resistance; cardiac output returns to pretreatment values, plasma volume remains slightly reduced, and plasma renin activity may be elevated.

During chronic administration, the antihypertensive effect of cyclopentiazide is dose dependent.

Like other diuretics, cyclopentiazide given as monotherapy achieves blood pressure control in about 40-50% of patients with mild to moderate hypertension.

Combination with oxprenolol potentiates the blood-pressure-lowering effect, making it possible to achieve a further decrease in blood pressure in a large proportion of patients who have failed to respond adequately to monotherapy.

5.2. Pharmacokinetic Properties

The active substances of Trasidrex show the same pharmacokinetic behaviour in the fixed combination as following simultaneous administration of Slow-Trasicor and Navidrex.

Oxprenolol

General characteristics

Absorption

In the gastrointestinal tract, oxprenolol is completely absorbed from the sustained-release tablets, regardless of whether or not they are taken together with food. Peak plasma concentrations are reached after an average of approx. 3 hours.

During treatment with sustained-release forms, prolongation of the absorption phase enables therapeutically active plasma concentrations to be maintained over a longer period of time than when the same doses are given in conventional dosage forms and avoids high peak drug concentrations in the plasma.

After the active substance has been absorbed, the insoluble matrix of the tablet is excreted in a softened form in the faeces.

Oxprenolol is subject to a first-pass effect. Its systemic bioavailability amounts to 20-70%.

Distribution

Oxprenolol has a plasma-protein binding rate of approx. 80% and a calculated distribution volume of 1.2 L/kg.

Oxprenolol crosses the placental barrier. The concentration in the breast milk is equivalent to approx. 30% of that in the plasma.

Elimination (biotransformation and excretion)

Oxprenolol has an elimination half-life of 1-2 hours.

Oxprenolol is extensively metabolised, direct O-glucuronidation being the major metabolic pathway and oxidative reactions minor ones. Oxprenolol is excreted chiefly in the urine (almost exclusively in the form of inactive metabolites).

Oxprenolol is not likely to accumulate.

Characteristics in patients

Age has no effect on the pharmacokinetics of oxprenolol.

In patients with acute or chronic inflammatory diseases an increase in the plasma levels of oxprenolol has been observed.

The plasma levels may also increase in the presence of severe hepatic insufficiency associated with a reduced metabolic rate.

Impaired renal function generally leads to an increase in the blood levels of oxprenolol, but the concentrations measured remain within - although at the upper limit of - the concentration range recorded in subjects with healthy kidneys. In addition, in patients with renal failure the apparent elimination half-life for unchanged, i.e. active, oxprenolol is comparable with the corresponding half-life values determined in subjects with no renal disease. Hence, there is no need to readjust the dosage in the presence of impaired renal function.

Cyclopenthiazide

General characteristics

After oral administration of single doses of 0.5 mg or 1 mg cyclopenthiazide, peak plasma levels of about 3 and 7 ng/mL respectively were reached after an average of 3-4 hours. Twelve hours after administration of 1 mg cyclopenthiazide, plasma concentrations fall to about 25% of the peak concentrations.

Thiazide diuretics cross the placental barrier and also pass into the breast milk.

Lipophilic thiazides also have a higher protein-binding rate, that of cyclopenthiazide amounting to approx. 92%. They therefore exert a more prolonged action than the more hydrophilic thiazides.

In humans receiving cyclopenthiazide, the drug can be detected in the urine. 24 hours after administration of 0.5 mg, for instance, concentrations in the urine are about 400 ng/mL.

Characteristics in patients

In patients with impaired renal function thiazides accumulate and uraemia may become more marked. Thiazide diuretics (including cyclopenthiazide) lose their diuretic effect when creatinine clearance is < 30 mL/min (or at serum creatinine levels of > 2.5 mg/100 mL.)

5.3. Preclinical Safety Data

None stated.

Pharmaceutical Particulars

6.1. List of Excipients

Core
Stearic acid
Aerosil R972
Povidone K25

Coat
avicel PH101
polyethylene glycol 6000
povidone K30
purified talc special
sucrose (granulated)
erythrosine aluminium lake.

Printing Ink
Black ink opacode S-1-8015

6.2. Incompatibilities

None known.

6.3. Shelf Life

60 months.

6.4. Special Precautions for Storage

Protect from heat, light and moisture. Store below 25°C.

6.5. Nature and Contents of Container

PVC/PVDC* Blister packs of 28 tablets.

*PVC 250 micron, PVDC 60 gsm, aluminium foil 20 micron.

6.6. Instruction for Use/Handling

None.

7. Marketing Authorisation Holder

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon

Surrey
CR0 0XT
UK

8. Marketing Authorisation Number

PL 12762/0217

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

06/03/2006

10 DATE OF REVISION OF THE TEXT

10/09/2007