SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TRASICOR Tablets 20 mg.
Oxprenolol 20 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxprenolol hydrochloride EP 20mg.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, round, biconvex, film-coated tablets, impressed OXP 20 on one face and no marking on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Angina Pectoris: For long-term prophylactic use (if necessary nitrates should be employed for alleviating acute attacks).

Hypertension: As monotherapy or for use in combination with other antihypertensives, e.g. with a diuretic, peripheral vasodilator, calcium channel blocker or ACE inhibitor.

Disturbances of cardiac rhythm: Especially supraventricular tachycardia, atrial fibrillation and digitalis-induced arrhythmias, ventricular tachycardia.

Short-term relief of functional cardiovascular disorders due to adrenergic hyperactivity: Such as cardiac neurosis, hyperkinetic heart syndrome and anxiety-induced cardiovascular disorders.

4.2 Posology and method of administration

The dosage should be individualised. Before raising the dosage, the heart rate at rest should always be checked. If it is 50-55 beats/min, the dosage should

not be increased, see contraindications. The tablets should be swallowed with liquid.

If the maximum recommended dose is insufficient to produce the desired response appropriate combined therapy should be considered.

When discontinuing prolonged treatment with a beta-blocker, the medication should not be interrupted abruptly, but withdrawn gradually.

Higher doses using conventional TRASICOR Tablets may be administered in two or more divided doses.

Elderly: No special dosage regime is necessary but concurrent hepatic insufficiency should be taken into account.

Children: No adequate experience has been acquired on the use of TRASICOR in children.

Hypertension: 80-160mg total daily dose, given in 2 to 3 doses. If necessary, the dosage can be raised to 320mg.

Angina pectoris: 80-160mg total daily dose, given in 2 to 3 doses. If necessary, the dosage can be raised to 320mg.

Distribution of cardiac rhythm: 40-240mg total daily dose given in 2-3 doses. The maximum recommended dose is 240mg/day.

Short-term relief of functional cardiovascular disorders due to adrenergic hyperactivity e.g. short-term relief of sympathomimetic symptoms of anxiety: 40-80mg daily, given in 1 or 2 doses, is usually sufficient.

4.3 Contraindications

Trasicor is contraindicated in patients with:

- Hypersensitivity to oxprenolol and related derivatives, cross-sensitivity to other beta-blockers or to any of the excipients.
- Cardiogenic shock.
- Second or third degree atrioventricular block.
- Uncontrolled heart failure.
- Sick-sinus syndrome.
- Bradycardia (<45 – 50bpm).
- Hypotension.
- Untreated phaeochromocytoma.
- Severe peripheral arterial circulatory disturbances.
- History of bronchospasm and bronchial asthma. (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).

- Use of anaesthetics which are known to have a negative inotropic effect.
- Metabolic acidosis.

4.4 Special warnings and precautions for use

Owing to the risk of bronchoconstriction, non-selective beta-blockers such as TRASICOR/SLOW TRASICOR should be used with particular caution in patients with chronic bronchitis or emphysema (see "Contraindications").

As beta-blockers increase the AV conduction time, beta-blockers should only be given with caution to patients with first degree AV block.

Beta-blockers should not be used in patients with untreated congestive heart failure. This condition should first be stabilised.

If the patient develops increasing bradycardia less than 50-55 beats per minute at rest and the patient experiences symptoms related to bradycardia, the dosage should be reduced or gradually withdrawn (see "Contraindications").

Beta-blockers are liable to affect carbohydrate metabolism. Diabetic patients, especially those dependent on insulin, should be warned that beta-blockers can mask symptoms 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 beta-blockers, particularly those who undergo prolonged fasting or severe exercise. The concurrent use of beta-blockers and anti-diabetic medication should always be monitored to confirm that diabetic control is well maintained.

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

Beta-blockers may reduce liver function and thus affect the metabolism of other drugs. Like many beta-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"). Patients with severe renal failure might be more susceptible to the effects of anthihypertensive drugs due to haemodynamic effects. Careful monitoring is advisable (see "Pharmacokinetic properties").

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

In patients with phaeochromocytoma a beta-blocker should only be given together with an alpha-blocker, (see "Contraindications").

Owing to the danger of cardiac arrest, a calcium antagonist of the verapamil type must not be administered intravenously to the patient already receiving treatment with a beta-blocker. Furthermore, since beta-blockers may potentiate the negative-inotropic and dromotropic effects of calcium antagonists, like verapamil or diltiazem, any oral comedication (e.g. in angina pectoris) requires close clinical control (see also "Interactions with other medicaments and other forms of interaction").

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, especially non-selective drugs, any may require higher than normal doses of adrenaline for treatment. Whenever possible, beta-blockers should be discontinued in patients who are at increased risk for anaphylaxis.

Especially in patients with ischaemic heart disease, treatment should not be discontinued suddenly. The dosage should gradually be 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 general anaesthetic to permit him to take the necessary precautions. The anaesthetic selected should be one exhibiting as little 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 beta-blocker should be withdrawn gradually at least 48 hours prior to surgery.

The full development of the "oculomucocutaneous 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 cleared after withdrawal of the treatment. Discontinuation of oxprenolol should be considered, and a switch to another antihypertensive drug might be advisable, see advice on discontinuation above.

4.5 Interaction with other medicinal products and other forms of interaction

Calcium channel blockers: e.g. verapamil, diltiazem: Potentiation of bradycardia, myocardial depression and hypotension; particularly after intravenous administration of verapamil in patients taking oral beta-blockers, the possibility of hypotension and cardiac arrhythmias cannot be excluded (see "Special Warnings and Precautions").

Class I anti-arrhythmic drugs and amiodarone: Drugs like disopyramide, quinidine and amiodarone may increase atrial-conduction time and induce negative inotropic effect when administered concomitantly with beta-blockers.

Sympathomimetic drugs: Non-cardioselective beta-blockers such as oxprenolol 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 non-selective beta-blockers, such as oxprenolol, treatment with clonidine should be continued for some time after beta-blocker has been discontinued to reduce the danger of rebound hypertension.

Catecholamine-depleting drugs: e.g. Guanethidine, reserpine, may have an additive effect when administered concomitantly with beta-blockers. Patients should be closely observed for hypotension.

Beta-blockers 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, causing hypotension and blocking tachycardia. In diabetic patients receiving beta-blockers 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 Precautions).

Non-steroidal anti-inflammatory drugs (NSAIDs): Non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the hypotensive effect of beta-blockade.

Cimetidine: Hepatic metabolism of beta-blockers may be reduced resulting in increased plasma levels of beta-blocker and prolonged serum half-life. Marked bradycardia may occur.

Ergot alkaloids: Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Anaesthetic drugs: beta-blockers and certain anaesthetics (e.g. halothane) are additive in their cardiodepressant effect. However, continuation of beta-blockers reduces the risk of arrhythmia during anaesthesia (see "Special Warnings and Precautions").

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

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

Alcohol and beta-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 TRASICOR are taken together (see also "Special Warnings and Precautions").

4.6 Pregnancy and lactation

As in the case of any form of drug therapy, oxprenolol should be employed with caution during pregnancy, especially in the first 3 months.

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

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

4.7 Effects on ability to drive and use machines

Patients receiving oxprenolol 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

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

Central nervous system:

Common: Fatigue, dizziness, headache, mental depression.

Uncommon: Sleep disturbances, nightmares.

Rare: Hallucinations, exertional tiredness.

Cardiovascular system:

Common: Hypotension, heart failure, peripheral vascular disorders (e.g. cold extremities, paraesthesia).

Uncommon: Bradycardia, disturbance of cardiac conduction.

Rare: Raynaud-like symptoms.

Gastro-intestinal tract:

Very common: Dry mouth, constipation.

Common: Nausea.

Uncommon: Diarrhoea, vomiting, flatulence.

Skin and appendages:

Uncommon: Allergic skin rash (e.g. urticarial, psoriasiform, eczematous, lichenoid).

Rare: Worsening of psoriasis.

Respiratory system:

Common: Dyspnoea, bronchoconstriction (see "Special Warnings and Precautions" and "Contra-indications").

Sense organs:

Uncommon: Visual disturbances ("blurred vision", "vision abnormal").

Rare: Dry eyes, keratoconjuctivitis.

Others:

Common: Disturbances of libido and potency.

Very rare: Thrombocytopenia.

4.9 Overdose

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

The manifestations of poisoning with beta-blocker 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.

Treatment: patients who are seen soon after potentially life-threatening overdosage (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, and electrolytes, and if

necessary, 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 beta-adrenergic receptors and it represents a useful alternative treatment for hypotension and heart failure.

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

For bronchospasm, aminophylline, salbutamol or terbutaline ($beta_2$-agonist) are effective bronchodilator drugs. Monitor the patient for dysrhythmias during and after administration.

Patients who recover should be observed for signs of beta-blocker withdrawal phenomenon (see "Special Warnings and Precautions").

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Oxprenolol, the active substance of TRASICOR, is a non-selective, lipophilic beta-blocker exerting a sympatholytic effect and displaying mild to modest partial agonistic activity (PAA), also known as intrinsic sympathomimetic activity (ISA).

Drugs like oxprenolol with PAA cause comparatively less slowing of the resting heart rate and a less marked negative-inotropic effect than those without PAA. The risk of substantial bradycardia at rest and heart failure is lessened.

The antiarrhythmic effect of oxprenolol is primarily due to suppression of the arrhythmogenic sympathetic influence of catecholamines. Evidence that increased sympathetic stimulation predisposes to many arrhythmias is strong. This is supported by the increased incidence of arrhythmias in man in situations associated with high sympathetic drive or myocardial sensitisation to catecholamines e.g. exercise, emotional stress, phaeochromocytoma, trauma, myocardial ischaemia, anaesthesia, hyperthyroidism.

Oxprenolol decreases cardiac impulse formation in the sinus node with resultant slowing of the sinus rate; it slightly prolongs the sino-artrial conduction time; both the atrio-ventricular (AV) conduction time and the AV node refractory periods are lengthened.

Some beta-blockers such as oxprenolol possess a membrane stabilising activity (MSA) on the cardiac action potential, also known as "quinidine-like" or "local anaesthetic" action, a property that tends to result in greater cardiac depression

than is seen with beta-blockers which do not have this pharmacological characteristic. However, at normal therapeutic doses, this property is probably clinically irrelevant and it only becomes manifest after overdose.

In coronary artery disease, oxprenolol is beneficial in increasing exercise tolerance and decreasing the frequency and severity of anginal attacks.

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

The exact way in which beta-blockers exert their antihypertensive action is still not fully understood. Various modes of action have been postulated. During chronic therapy the antihypertensive effect of beta-blockers is associated with a decline in peripheral resistance.

Oxprenolol is effective in lowering elevated supine, standing and exercise blood pressure; postural hypotension is unlikely to occur.

5.2 Pharmacokinetic properties

Absorption: Oral oxprenolol is rapidly and completely absorbed. Food has no significant effect on absorption. Peak plasma concentrations are achieved approximately 1 hour after drug administration.

Biotransformation: Oxprenolol is subject to first-pass metabolism. Its systemic bioavailability is 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: 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). The drug 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 metabolism.

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.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium phosphate tribasic, magnesium stearate, polyvinylpyrollidone K25, sucrose, purified talc special, wheat starch, cellulose-HP-M-603, Kollidon VA64, titanium dioxide E171.

6.2 Incompatibilities

None known

6.3 Shelf life

60 months

6.4 Special precautions for storage

Protect from moisture

6.5 Nature and contents of container

PVC* Blister packs of 56 and 100 tablets
*PVC 250micron, aluminium foil 20 micron

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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