1. NAME OF THE MEDICINAL PRODUCT

Slow Trasicor 160 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 160 mg of oxprenolol hydrochloride.

Excipients with known effect:
- Lactose crystalline (BP DC Sperolac 100) (35 mg/tablet)
- Lactose granules (Granulac 200) (132 mg/tablet + 1.752 mg/tablet coating)
- Glycerol palmitostearate (EP type 1, Precirol AT05) (10 mg/tablet)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablets

White, round, slightly biconvex, coated tablets with bevelled edges and the imprint ‘SLOW TRASICOR’ on one side.

4.1 Therapeutic indications

Slow Trasicor Tablets are indicated in adults for the treatment of:

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

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

4.2 Posology and method of administration

Posology

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.

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When discontinuing prolonged treatment with a beta-blocker, the medication should not be interrupted abruptly, but withdrawn gradually.

The sustained-release formulation provides a longer pharmacological action from a given dose, thus allowing once daily administration. When the dose is raised to more than one Slow Trasicor tablet, it is usual for this to continue to be given once daily.

Oxprenolol is only gradually released from the sustained-release tablet, extending the duration of effect. The occurrence of high peak concentrations in the plasma is thus avoided.

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

**Paediatric population**
No adequate experience has been acquired on the use of Slow Trasicor Tablets in children.

**Adults**
Hypertension: 160 mg once daily. If necessary, the dosage can be raised to 320 mg.

Angina pectoris: 160 mg once daily. If necessary, the dosage can be raised to 320 mg.

**Method of administration**
Slow Trasicor Tablets should be swallowed whole with liquid.

### 4.3 Contraindications

- Hypersensitivity to oxprenolol and related derivatives, cross-sensitivity to other beta-blockers or to any of the excipients listed in section 6.1.
- Cardiogenic shock.
- Second or third degree atrioventricular block.
- Uncontrolled heart failure.
- History of cor pulmonale.
- Sick-sinus syndrome.
- Bradycardia (< 45–50 bpm).
- 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)
- Chronic obstructive pulmonary disease.
- Prinzmetal's angina (variant angina pectoris).
- Use of anaesthetics which are known to have a negative inotropic effect.
- Metabolic acidosis.
• Prolonged fasting.
• Severe renal failure.

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.

4.4 Special warnings and precautions for use

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.

As with all beta-blockers, oxprenolol should be used with caution in patients with a recent myocardial infarction.

Beta-blockers may unmask myasthenia gravis.

Caution is advised in patients with psoriasis, as oxprenolol can worsen this condition (see section 4.8).

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 section 4.3).

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 section 4.5). 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 patient 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 section 5.2).
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 (see section 5.2). 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 due to haemodynamic effects particularly patients with severe renal failure (see section 4.3).

In patients with peripheral circulatory disorders (e.g. Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur (see section 4.3).

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

In patients with phaeochromocytoma a beta-blocker should only be given together with an alpha-blocker, (see section 4.3).

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 (see section 4.3). Furthermore, since beta-blockers may potentiate the negative-inotropic and dromotropic effects of calcium antagonists, like verapamil or diltiazem, any oral co-medication (e.g. in angina pectoris) requires close clinical control (see also section 4.5).

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, especially non-selective drugs, and 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. During treatment with oxprenolol, patients should not undergo anaesthesia with agents causing myocardial depression (e.g. cyclopropane, trichloroethylene, ether, chloroform). If on the other hand, inhibition of sympathetic tone during the operation is regarded as undesirable, the betablocker 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.

Interference with laboratory tests:
Oxprenolol use may give falsely high fluorometric readings in urine cortisol determinations.

Slow Trasicor Tablets contain lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Slow Trascor Tablets contain glycerol
May cause headache, stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

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

Calcium channel blockers: Oxprenolol should not be used with calcium-channel blockers with negative inotropic effects e.g. verapamil and to a lesser extent diltiazem. The concomitant use of oral beta-blockers and calcium antagonists of the dihydropyridine type can be useful in hypertension or angina pectoris. However, because of their potential effect on the cardiac conduction system and contractility, the i.v. route must be avoided. The concomitant use with dihydropyridines e.g. nifedipine may increase the risk of hypotension. In patients with cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure (see section 4.3 and 4.4).

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. Beta-blockers may decrease the clearance of theophylline.

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.

Monoamine oxidase inhibitors: concurrent use with beta-blockers is not recommended. Possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the MAO inhibitor. Blood pressure and heart rate should be monitored more closely in patients taking this medicine with a MAO inhibitor.

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 section 4.4). 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 section 4.4).

Non-steroidal anti-inflammatory drugs (NSAIDs): Non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, 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 and hypertension during anaesthesia (section 4.4).

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 Slow Trasicor Tablets are taken together (see also “Special Warnings and Precautions”).
Barbiturates and rifampicin can increase the metabolism of some beta-blockers (resulting in reduced plasma levels).

Hydralazine can decrease the metabolism of some beta-blockers (resulting in increased plasma levels).

Antimalarials such as mefloquine can cause arrhythmias and caution is necessary if used with beta-blockers.

Concomitant use of beta-blockers with phenothiazines may increase the blood pressure lowering effect.

Excessive caffeine and nicotine intake may oppose the beneficial effects of oxprenolol. The hypotensive effects of tricyclic antidepressants may be exacerbated in patients receiving beta-blockers.

Concomitant administration of sulfinpyrazone with oxprenolol may reduce or abolish its antihypertensive effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
Oxprenolol should not be given during pregnancy unless there are no safer alternatives. 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.

Breast-feeding
Oxprenolol is excreted into breast milk (see section 5.2). 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 section 4.8) 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Very rare: Thrombocytopenia sometimes with purpura.
Not known: Agranulocytosis.

Metabolism and nutrition disorders
Not known: Diabetes mellitus, hypoglycaemia, hyperglycaemia.

Psychiatric disorders
Common: Depression, libido disorder.
Uncommon: Sleep disorder, nightmares.
Rare: Hallucinations.
Not known: Psychosis, confusional state.

Nervous system disorders
Common: Headache, dizziness.

Eye disorders
Uncommon: Visual impairment (vision blurred, vision abnormal).
Rare: Dry eyes, keratoconjunctivitis.

Cardiac disorders
Common: Cardiac failure.
Uncommon: Bradycardia, cardiac conduction disorders.
Not known: Complete atrioventricular block, cardiac arrhythmia.

Vascular disorders
Common: Hypotension, peripheral vascular disorders (e.g. peripheral coldness, paraesthesia).
Rare: Raynaud’s phenomenon.
Not known: Necrotising vasculitis, intermittent claudication.

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, bronchospasm (see section 4.3 and 4.4).

Gastrointestinal disorders
Very common: Dry mouth, constipation.
Common: Nausea.
Uncommon: Diarrhoea, vomiting, flatulence.
Not known: Abdominal discomfort, retroperitoneal fibrosis, dyspepsia.
Musculoskeletal and connective tissue disorders
Not known: Myalgia, arthralgia, muscle cramps, myasthenia gravis.

Skin and subcutaneous tissue disorders
Uncommon: Dermatitis allergic.
Rare: Worsening of psoriasis.
Not known: Rash, toxic epidermal necrolysis, cutaneous lupus erythematosus like lesions, reactivation of cutaneous lupus erythematosus, pruritus, hyperhidrosis.

Reproductive system and breast disorders
Common: Erectile dysfunction.

Renal and urinary disorders
Not known: Glycosuria.

General disorders and administration site conditions
Common: Fatigue.
Rare: Exertional tiredness.
Not known: Hyperpyrexia.

Investigations
Not known: An increase in ANA (anti-nuclear antibodies) has been seen; its clinical relevance is not clear.

Chronic treatment with oxprenolol increases very low density lipoprotein and decreases high density lipoprotein, which may have an adverse effect on the risk of cardiovascular events.

Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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. Rhabdomyolysis with myoglobinuria has been reported as a complication of severe overdosage with oxprenolol.

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.

Management
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 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 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 (beta2-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 section 4.4).

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agent, non selective
ATC code: C07AA

Oxprenolol, the active substance of Slow Trasicor Tablets, 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-atrial 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:
In the gastrointestinal tract, oxprenolol is rapidly and completely absorbed from the sustained release tablets, regardless of whether or not they are taken together with food. Peak plasma concentrations are attained after an average of approximately 3 hours.

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

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.

Oxprenolol is moderately lipid-soluble and crosses the blood-brain barrier.

**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

6.1 **List of excipients**

Silicon dioxide (Aerosil 200)
Calcium stearate
Methacrylic acid copolymer
Lactose crystalline (BP DEC Sperolac 100)
Lactose granules (Granulac 200)
Glycerol palmitostearate

Coating
Cellulose HP-M-603 (Hypromellose 3cps)
Methacrylic acid copolymer (Eudragit NE40D)
Lactose granules (Granulac 200)
Magnesium stearate
Polysorbate 80
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

None

6.5 Nature and contents of container

PVC* Blister packs of 28 tablets *PVC 250micron, aluminium foil 20 micron

6.6 Special precautions for disposal and other handling

None.

7 MARKETING AUTHORISATION HOLDER

Amdipharm UK Limited
Regency House
Miles Gray Road
Basildon
Essex
SS14 3AF
United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0017

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