Corbeton

Oxprenolol hydrochloride

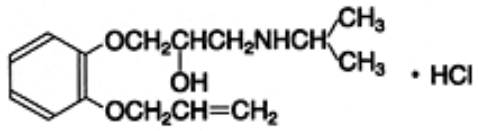
PRODUCT INFORMATION

Name of the Medicine

The active ingredient of Corbeton is Oxprenolol hydrochloride.

The chemical name for Oxprenolol hydrochloride is 1-(2-allyloxyphenoxy)-3-isopropylamino-propan-2-ol hydrochloride.

Its structural formula is:



Molecular formula:	Molecular weight:	CAS Registry No.:
$C_{15}H_{23}NO_3HCl$	301.85	6452-73-9

Description

Oxprenolol is a nonselective beta-adrenoreceptor antagonist possessing partial agonist effect (intrinsic sympathomimetic activity).

Pharmacology

Oxprenolol exerts a competitive and reversible inhibitory effect on autonomic beta-adrenergic receptors. Cardiac effects include reduction of tachycardia due to sympathetic stimulation and circulatory pressor amines, myocardial oxygen requirement is reduced and, particularly in cases of angina pectoris, improvement in effort tolerance is observed.

Certain arrhythmias may respond favourably to beta-blockade, including sinus tachycardia (e.g. due to hyperthyroidism), paroxysmal supraventricular tachycardia and extrasystoles. In atrial flutter and fibrillation, the ventricular rate is usually reduced and sinus rhythm may be restored.

In addition, oxprenolol possesses membrane stabilising ability ("quinidine-like effects") which may contribute to the antiarrhythmic action.

Following administration to hypertensive patients, oxprenolol produces a gradual and sustained reduction in systolic and diastolic blood pressure. Maximum effect from a given dosage develops gradually and periods of up to 4 weeks may elapse before full benefit is obtained. Oxprenolol rarely causes postural hypotension when the dose is increased gradually.

Pharmacokinetics

After oral administration of a solution or conventional tablets, 70 to 90% of the single dose is absorbed and peak plasma concentration is reached in 0.5 to 1.5 hours.

The absorption of oxprenolol is not significantly affected by the presence of food in the stomach.

The bioavailability of the oral formulation is 24 to 60%. A dose-dependent first-pass effect has not been observed.

The volume of distribution of oxprenolol is 1.3 L/kg.

Approximately 80% of oxprenolol in plasma is bound to plasma protein (*in vitro*).

Oxprenolol is extensively metabolised by the liver.

Between 70 and 95% of an oral dose is excreted in the urine, 2 to 5% being unchanged oxprenolol. Total body clearance is 0.6 L/minute.

The elimination half-life of oxprenolol is approximately 1 to 2 hours.

Indications

Angina pectoris.

Cardiac arrhythmias (including those due to digitalis intoxication).

Sinus tachycardia of various origins (e.g. hyperthyroidism), paroxysmal atrial tachycardia, supraventricular and ventricular extrasystoles.

Hypertension.

Contraindications

1. *Bronchospasm.* Beta-adrenergic blockade of the smooth muscle of bronchi and bronchioles may result in an increased airways resistance. These drugs also reduce the effectiveness of asthma treatment. This may be dangerous in susceptible patients. Therefore, beta-blockers are contraindicated in any patient with a history of airways obstruction or a tendency to bronchospasm. Use of cardioselective beta-blockers can also result in severe bronchospasm. If such therapy must be used, great caution should be exercised. Alternative therapy should be considered.

2. Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm.

3. Right ventricular failure secondary to pulmonary hypertension.

4. Significant right ventricular hypertrophy (except in specific cases of congenital heart disease, e.g. tetralogy of fallot, at the discretion of a cardiologist).

5. Sinus bradycardia (less than 45-50 beats/minute) or sick sinus syndrome.

6. Second and third degree A-V block.

7. Shock (including cardiogenic and hypovolaemic shock).

8. Hypersensitivity to the drug.

Warnings

1. *Cardiac failure.* Beta-blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency or unsuspected cardiomyopathy. In patients without a history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If cardiac failure develops, Corbeton should be withdrawn (see Warnings 2). (***Note.*** Although congestive heart failure has been considered to be a contraindication to the use of beta-blockers, there is a growing literature on the experimental use of beta-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs, beta-blockers should not normally be prescribed for heart failure outside of specialist centres.)

2. *Abrupt withdrawal.* Care should be taken if beta-blockers have to be discontinued abruptly in patients with coronary artery disease. Severe exacerbation of angina and precipitation of myocardial infarction and ventricular arrhythmias has occurred following abrupt discontinuation of beta-blockade in patients with ischaemic heart disease. Therefore it is recommended that the dosage be reduced gradually over a period of about 8 to 14 days during which time the patient's progress should be assessed. The drug may be reinstituted temporarily if the angina worsens. If the drug must be withdrawn abruptly, close observation is required. In the peri-operative period, beta-blockers should not be withdrawn, unless there are strong clinical reasons to do so.

3. *Concomitant therapy with calcium antagonists.* The concomitant use of beta-blockers and calcium antagonists with myocardial depressant and sinus node activity, e.g. verapamil and, to a lesser extent, diltiazem, may cause hypotension, bradycardia and asystole. Extreme caution is required if these drugs have to be used together.

   The dihydropyridine calcium antagonists (e.g. nifedipine) have a weaker myocardial depressant effect and can be administered cautiously with beta-blockers. If excessive hypotension develops, the calcium antagonist should be stopped or the dosage reduced.

4. *Peripheral circulation.* Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease.

5. *Antiarrhythmic drugs.* Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lidocaine; Class IC agents, flecainide and propaferone (not available in Australia); the Class III agent, amiodarone; and the Class IV antiarrhythmic agents.

6. *Prinzmetal angina.* There is a risk of exacerbating coronary artery spasm if patients with Prinzmetal or variant angina are treated with a beta-blocker. If this treatment is essential, it should only be undertaken in a Coronary or Intensive Care Unit.

7. *Euthyroid hyperthyroxinaemia.* The effects of beta-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T_4) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Precautions

1. *Anaesthesia and the peri-operative period.* Beta-blockade may have beneficial effects in decreasing the incidence of arrhythmias and myocardial ischaemia during anaesthesia and the post-operative period. It is currently recommended that maintenance beta-blockade be continued peri-operatively. The anaesthetist must be made aware of beta-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia.

   Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported. Modern inhalational anaesthetic agents are generally well tolerated, although older

agents (ether, cyclopropane, methoxyflurane, trichlorethylene) were sometimes associated with severe circulatory depression in the presence of beta-blockade.

2. *Diabetes.* Beta-blockers affect glucose metabolism and may mask some important premonitory signs of acute hypoglycaemia, such as tachycardia.

   In patients with insulin or non-insulin dependent diabetes, especially labile diabetes, or with a history of spontaneous hypoglycaemia, beta-blockade may result in the loss of diabetic control and delayed recovery from hypoglycaemia. The dose of insulin or oral hypoglycaemic agent may need adjustment.

3. *Other metabolic effects.* Beta-adrenoreceptors are involved in the regulation of lipid as well as carbohydrate metabolism. Some drugs affect the lipid profile adversely, although the long-term clinical significance of this change is unknown and the effect appears to be less for drugs with intrinsic sympathomimetic activity.

4. *Renal disease.* In patients with severe renal disease, haemodynamic changes following beta-blockade may impair renal function further. Beta-blockers which are excreted mainly by the kidney may require dose adjustment in patients with renal failure.

5. *Use of catecholamine-depleting agents.* Concomitant use of drugs such as reserpine and guanethidine requires careful monitoring since the added effect of beta-blockade may produce an excessive reduction of the resting sympathetic nervous tone.

6. *Clonidine.* Concurrent use of beta-blockers and clonidine should be avoided because of the risk of adverse interaction and severe withdrawal symptoms. If administered concomitantly, the clonidine should not be discontinued until several days after the withdrawal of the beta-blocker.

7. *Phaeochromocytoma.* In patients with this condition, an alpha-blocking drug (e.g. phentolamine/ phenoxybenzamine) should be administered before the beta-blocker to avoid exacerbation of hypertension.

8. *Eye and skin reactions.* Various skin rashes and conjunctival xeroses have been reported with beta-blockers. Cross-reactions may occur between beta-blockers, therefore substitutions within the group may not necessarily preclude occurrence of symptoms.

9. *Allergic conditions.* These may be exaggerated by beta-blockade (e.g. allergic rhinitis during the pollen season and allergic reactions to bee and wasp stings). Beta-blockers should be avoided if there is a risk of bronchospasm.

10. *Hyperthyroidism.* Because beta-blockers may mask the clinical signs of developing or continuing hyperthyroidism, resulting in symptomatic improvement without any change in thyroid hormone status, special care should be exercised in those patients who are hyperthyroid and are also receiving beta-blockers.

Use in Pregnancy (Risk Category: C)

Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the fetus and newborn infant.

Use in Lactation

Oxprenolol is excreted in breast milk but it is not known whether it is harmful to the newborn. Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risks.

Interactions with other medicines

Severe hypertension has been reported in one patient receiving phenylpropanolamine with methyldopa and oxprenolol.

Concurrent overdoses of potassium and beta-blocking drugs may lead to severe hypertension.

Drugs which inhibit calcium transport (e.g. verapamil) are contraindicated as arrhythmias and cardiac arrest have been reported.

Monoamine oxidase inhibitors (MAOIs) used concomitantly with beta-blockers may result in an exaggerated response to biogenic amines.

The inotropic action of digitalis may be reduced by beta-blocker action. The effects of beta blockers and digitalis are active in depressing atrioventricular conduction.

See also Precautions.

Adverse Effects

More common effects. Side effects such as exertional tiredness, headache, insomnia, vivid dreams, dizziness, depression, gastrointestinal upsets (indigestion, nausea, colic, diarrhoea) may be encountered, especially at the start of treatment. Most of these side effects are attributable to the drug's effect on extracardiac beta-adrenergic receptors. They usually prove transient and are seldom severe enough to necessitate reduction of dosage or interruption of the medication.

Less common effects. In rare cases, hypersensitivity reactions (e.g. itching and reddening of the skin), feelings of coldness in the extremities, thrombocytopenia, bradycardia, palpitations, postural hypotension, hypoglycaemia, excessive perspiration, joint pains, trigeminal neuralgia, double vision, ocular and cutaneous symptoms, and a schizophrenia-like psychosis have been reported.

Serious or life threatening effects. Severe adverse reactions such as bronchospasm, hypotension and cardiac failure may occur, particularly in association with overdosage.

Dosage and Administration

Corbeton tablets should be swallowed whole and taken with liquid.

Angina pectoris. Commence therapy with 20 or 40 mg three times daily. This dosage may be adequate but can be increased if necessary, (e.g. up to 320 mg daily).

Cardiac arrhythmias and tachycardia. Treatment may be initiated with 20 mg two or three times a day, increasing to 80 mg daily if necessary. For maintenance therapy, 20 mg daily may be satisfactory.

Hypertension. In monotherapy, commence treatment with 40 to 80 mg twice daily and increase the dose at weekly intervals by increments of up to 160 mg until a satisfactory response is obtained. For maintenance treatment, a daily dosage of 160 to 320 mg usually proves adequate. There is seldom anything to be gained by administering monotherapy in higher doses, since virtually no increase in the response can be achieved by this means.

Twice daily dosage (morning and early evening) is the optimum for oxprenolol therapy, but if the daily dosage is 160 mg or less, it may be given as a single daily dose to be taken in the morning.

In moderate to severe hypertension, oxprenolol is frequently combined with a thiazide or thiazide type diuretic agent. Mutual potentiation of antihypertensive effects allows the dose of beta-blocker to be reduced.

Corbeton should be administered only under strict medical supervision.

Overdosage

Symptoms. This may be evident by excessive bradycardia, hypotension, bronchoconstriction or cardiac failure.

Treatment. Treatment of early cases necessitates temporary suspension of Corbeton with ultimate readjustment of dosage. Where serious overdosage is associated with marked bradycardia and hypotension, intravenous atropine 1 to 2 mg should be given (repeated if necessary) and followed by intravenous isoprenaline hydrochloride. An infusion using 1,000 microgram of isoprenaline hydrochloride in 200 mL of 5% glucose may be administered at the rate of 1 mL (5 microgram) per minute until the desired effect has been achieved. Glucagon can also be given. Cardiac failure may require digitalisation in conjunction with diuretic therapy.

In cases of overdosage, it is advisable to contact the Poisons Information Centre (131126) for recommendation on the management and treatment of overdosage.

Presentation and Storage Conditions

Corbeton 20, 20 mg tablet: white, clear coated, marked $\frac{\text{OL}}{20}$ on one side, α on the reverse; 100's

Corbeton 40, 40 mg tablet: white, clear coated, marked $\frac{\text{OL}}{40}$ on one side, α on the reverse; 100's

Store below 30°C.

Poison Schedule of Medicine

S4 – Prescription Only Medicine

Name and Address of the Sponsor

Alphapharm Pty Limited
Chase Building 2
Wentworth Park Road
Glebe NSW 2037

ABN 93 002 359 739

www.alphapharm.com.au

Date of Approval

Approved by the Therapeutic Goods Administration on 5 May 1994.

Date of most recent amendment: 19 January 2007.