



APO-TIMOL

1. PRODUCT NAME

APO-TIMOL (10mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg timolol maleate 10mg equivalent to 10mg timolol.

Excipient(s) with known effect

APO-TIMOL contains lactose, FD&C Blue No. 1 and FD&C Blue No. 2.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

APO-TIMOL tablets are round, light blue, flat-faced, bevelled-edged tablets. Scored and engraved T10 on one side, other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Timolol is indicated for patients with:

- Essential hypertension including the hyperkinetic heart syndrome
- the management of atrial fibrillation or flutter.
- angina pectoris due to ischaemic heart disease.
- prophylaxis of common or classical migraine.
- ischaemic heart disease to reduce the risk of cardiac death, including sudden death, and re-infarction in those who have survived the acute phase of myocardial infarction.

4.2 Dose and method of administration

Dose

Hypertension:

Therapy should be initiated with a daily single or divided oral dose of 10mg, increasing to a maximum daily dose of 60mg, subject to the patient's response. Daily dosages above 20mg should be administered on a divided dose schedule. Timolol may also be used with thiazides, hydralazine, or methyldopa, although dosage adjustments are usually required. For concomitant use with catecholamine-depleting medicines such as reserpine or guanethidine (see section 4.4 Special Warnings and Precautions for Use. When Timolol is administered concomitantly with hydrochlorothiazide and amiloride hydrochloride, most patients will respond to a regimen of 10 or 20mg of timolol given orally once daily and one tablet of 50mg hydrochlorothiazide/5mg amiloride hydrochloride.

Angina:

Therapy should begin with a single oral dose of 5mg taken two or three times daily. Increases in dosage may be necessary with the first increase not exceeding 10mg per day in divided doses and subsequent increases should not exceed 15mg per day in divided doses. There should be an interval of at least three days between increases in dosage. The usual dosage range of timolol tablets is 15 to 45mg daily, with the majority of patients responding to a daily dosage of 35 to 45mg.

Ischaemic Heart Disease:

Timolol tablets may be administered in a single dose of 10mg taken twice daily for long-term prophylaxis in patients who have survived the acute phase of a myocardial infarction.

Atrial Fibrillation:

Therapy may be initiated with a single oral dose of 10mg taken twice daily, increasing to 30mg twice daily, subject to the clinical response.

Migraine:

Timolol tablets may be administered in single doses of 10 to 20mg daily for the prophylactic treatment of common and classic migraine.

Renal insufficiency:

Dosage adjustments may be necessary.

Paediatric population:

Timolol tablets are not suitable for children

Method of administration

The tablets are for oral administration.

Maximum Tolerated Daily Dose

Timolol maximum tolerated daily dose is 60mg

4.3 Contraindications

Timolol is contraindicated in:

- hypersensitivity to any component of this product
- bronchial asthma or other obstructive lung disorders or bronchospasm
- uncontrolled heart failure
- cardiogenic shock
- sick sinus syndrome
- grade 2 and 3 AV block and infra nodal AV block
- severe bradycardia

4.4 Special warnings and precautions for use

Bradycardia:

Severe sinus bradycardia due to unopposed vagal activity may result from the administration of timolol, and may be countered by intravenous administration of atropine, or if bradycardia persists, intravenous administration of isoprenaline.

Cardiac failure:

Timolol therapy may promote cardiac failure in patients with or without a history of cardiac disease. However, timolol may be cautiously administered to patients with a history of failure who are well-compensated, usually with digoxin and diuretics. Patients developing signs of heart failure should be fully digitalised and/or given a diuretic. Concomitant administration of timolol with digoxin may reduce, but not abolish, the inotropic effect of digoxin, and there may be additive effects of decreased A-V nodal conduction. If cardiac failure persists, timolol should be withdrawn.

Thyrototoxicosis:

Beta-blocker therapy may mask the signs of hyperthyroidism. Acute manifestations such as thyroid storm may develop upon abrupt withdrawal.

Withdrawal:

Timolol treatment should not be abruptly withdrawn from patients presenting symptomatic or asymptomatic ischaemic heart disease. Myocardial infarction, ventricular arrhythmias, or sudden death have been reported in such patients following the abrupt cessation of beta adrenoceptor blocker therapy, with or without preceding exacerbation of angina pectoris. Dosage levels of timolol should be gradually reduced over about two weeks while maintaining the same frequency of administration, and the patient should be carefully observed. Timolol therapy should be reinstated, at least temporarily for patients presenting angina pectoris, if the angina still markedly worsens, or for any patient if acute coronary insufficiency develops.

Diabetes mellitus:

Timolol should be cautiously administered to patients prone to spontaneous hypoglycaemia or those receiving anti-diabetic therapy since hypoglycaemia may be precipitated during fasting. Attendant symptoms of tachycardia and tremor may be masked but dizziness and sweating are unaffected and can serve as warning signs of hypoglycaemia.

Kidney and liver impairment:

Timolol should be cautiously administered to patients presenting renal insufficiency or liver impairment, and should be accompanied by routine laboratory tests to monitor function. Patients with severe renal insufficiency undergoing renal haemodialysis have developed significant hypotension following oral administration of 20mg timolol. Dosage reductions may be necessary when hepatic and/or renal insufficiency is present.

Respiratory diseases:

Timolol should be cautiously administered to patients prone to non-allergic bronchospasm from chronic bronchitis or emphysema since it may block catecholamine stimulated bronchodilation.

Surgery:

Timolol treatment poses a considerable risk to the patient during surgery. Some patients receiving Timolol have been subject to protracted severe hypotension during anaesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. However, abrupt withdrawal of timolol may promote severe complications.

Muscle Weakness:

Timolol has been reported, on rare occasions, to increase muscle weakness in some patients with myasthenic symptoms.

Cerebrovascular Insufficiency:

Timolol should be used with caution in patients with cerebrovascular insufficiency due to the potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse. If signs or symptoms suggesting a reduced cerebral blood flow are observed, consideration should be given to discontinuing these agents.

Risk from Anaphylactic Reaction:

While taking timolol patients with a history of atopy of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic or therapeutic. These patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

4.5 Interaction with other medicines and other forms of interaction

Calcium antagonists:

Concomitant administration of timolol with calcium antagonists may promote hypotension, A-V conduction disturbances, and left ventricular failure, particularly in patients with impaired cardiac function. The nature of the interaction appears to be structure specific; hypotension may result from the combination of timolol with dihydropyridine derivatives, such as nifedipine, verapamil and A-V conduction disturbances or left ventricular failure may result from the combination of timolol with diltiazem or nifedipine. The combination of timolol and digoxin with either diltiazem or verapamil may have additive effects in prolonging A-V conduction time. Intravenous calcium entry blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

Nonsteroidal anti-inflammatory medicines:

These medicines may counter the antihypertensive effects of timolol by promoting sodium and fluid retention through inhibition of renal prostaglandin synthesis.

Catecholamine-depleting agents:

The patient should be closely observed when timolol is administered with catecholamine-depleting agents like reserpine, due to the possible additive effects and the onset of hypotension and/or marked bradycardia, which can cause vertigo, postural hypotension or syncope.

Digitalis:

The use of beta-adrenergic blocking agents and digitalis with either verapamil or diltiazem may have additive effects in prolonging AV conduction time.

Clonidine:

Following the withdrawal of clonidine, the beta-adrenergic blocking agent may increase the likelihood of rebound hypertension. If Timolol and Clonidine are co-administered, the beta-adrenergic blocking agent should be withdrawn several days before the gradual withdrawal of clonidine. If beta-blocker therapy is replacing clonidine, then the introduction of beta-adrenergic blocking agents should be delayed by several days after clonidine administration has ceased.

Quinidine:

During combined treatment with Quinidine and timolol there have been reports of potentiated systemic beta-blockade (e.g. Decreased heart rate). This could be due to the quinidine inhibiting the metabolism of timolol via the P-450 enzyme, CYP2D6.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C

There are no well controlled studies in pregnant women. Respiratory depression, neonatal bradycardia and hypoglycaemia have been associated with Timolol therapy of the pregnant mother.

Timol should only be used during pregnancy if the potential benefits outweigh the potential risks to the foetus.

Lactation

Timolol is detectable in human milk. Due to the potential of serious adverse reactions in infants, a decision should be made whether to discontinue nursing or to discontinue Timolol therapy, taking into account the importance of the medication to the mother.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for nervous system and visual effects such as nervousness, dizziness, vertigo, paraesthesia, local weakness, diminished concentration, hallucinations, depression, somnolence, visual disturbances, diplopia, ptosis, eye irritation, and dry eyes and advised not to drive or operate machinery if these symptoms occur or until their individual susceptibility is known.

Likely to produce minor or moderate adverse effects on the ability to drive or use machinery.

4.8 Undesirable effects

Summary of the safety profile

Most adverse effects reported have been mild and transient.

Tabulated list of adverse reactionsSystem Order Class	Undesirable Effect
Blood and lymphatic system disorders	Non thrombocytopaenic purpura
Endocrine disorders	Hyperglycaemia, hypoglycaemia
Nervous system disorders	Headache, nervousness, dizziness, vertigo, paraesthesia, local weakness, diminished concentration, increased dreaming, hallucinations, nightmares, insomnia, depression, somnolence, and decreased libido
Eye disorders	Visual disturbances, diplopia, ptosis, eye irritation, and dry eyes
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Chest pain, bradycardia, cardiac arrest, palpitation, arrhythmia, AV block, hypotension, cardiac failure
Vascular disorders	cerebral vascular accident, Raynaud's phenomenon, syncope, cold extremities, claudication, hypotension, oedema, pulmonary oedema, exacerbated arterial insufficiency, exacerbated angina pectoris, and vasodilation
Respiratory, thoracic and mediastinal disorders	Dyspnoea, bronchial spasm, rales, and cough.
Gastrointestinal disorders	Dyspepsia, nausea, vomiting, diarrhoea, and hepatomegaly.
Skin and subcutaneous tissue disorders	Rash, pruritus, skin irritation, increased pigmentation, sweating, and exfoliative dermatitis.
Musculoskeletal and connective tissue disorders	extremity pain, Arthralgia
General disorders and administration site conditions	Asthenia, fatigue, decreased exercise tolerance
Investigations	Slight increases in blood urea nitrogen, serum potassium, serum uric acid and triglycerides and slight decreases in haemoglobin, haematocrit and HDL-cholesterol may occur with timolol therapy, but these are not progressive or associated with clinical manifestations.

Associated adverse events based on experience with medicines of the same class

Other adverse effects seen with other beta-adrenergic blocking agents but not observed in clinical trials are listed below and should be considered as potential adverse effects of APO-TIMOL.

Central nervous system:

Reversible mental depression progressing to catatonia, an acute reversible syndrome characterised by: - Emotional lability, short-term memory loss, disorientation from time and place, slightly clouded sensorium and decreased performance on neuropsychometrics.

Gastrointestinal:

Mesenteric arterial thrombosis, ischaemic colitis.

Haematologic:

Thrombocytopaenic purpura, agranulocytosis

Allergic:

Fever combined with aching and sore throat, erythematous rash, laryngospasm and respiratory distress.

Miscellaneous:

Peyronie's disease, reversible alopecia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

No data is available in regard to overdosage in humans.

The most common signs and symptoms to be expected with overdosage are symptomatic bradycardia, hypotension, bronchospasm, and acute cardiac failure.

If overdosage does occur then treatment should be withdrawn and symptomatic treatment should be initiated, and the patient being observed closely.

Gastric lavage may be of benefit.

Anticholinergic agents such as atropine 0.25 to 2mg intravenous may be used as antidotes to relieve bradycardia. If bradycardia persists, isoprenaline may be administered intravenously with caution, although refractory cases may necessitate the issue of a cardiac pacemaker.

Heart failure may be treated by conventional therapy with digitalis, diuretics and oxygen being instituted immediately.

Severe hypotension may be treated by cautious administration of noradrenaline, dopamine or dobutamine. In refractory cases the use of intravenous aminophylline is suggested. If necessary this can be followed glucagon hydrochloride which has been reported to be useful.

Beta adrenergic agonist, isoprenaline may be used as antidotes to relieve bronchospasm. Additional therapy with aminophylline may be considered. Isoprenaline or a cardiac pacemaker can be used to relieve heart block.

Hypoglycaemia may be treated by intravenous glucose infusions.

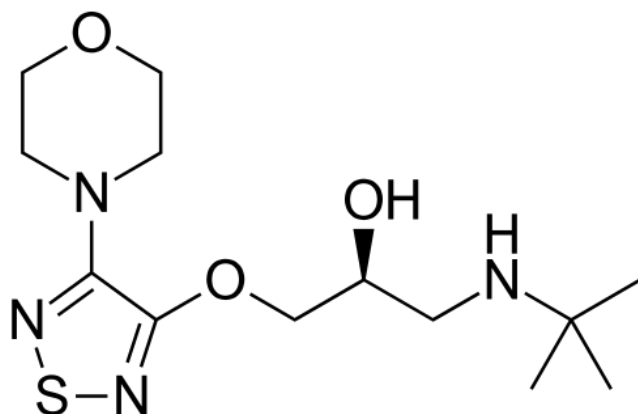
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: hydrophilic non-cardio selective beta-adrenergic blocking agent

ATC code: C07BA06

Chemical Structure:



Molecular Formula:

C₁₇H₂₈N₄O₇S

Mechanism of action

Timolol is a hydrophilic non-cardio selective beta-adrenergic blocking agent. It is reported to lack intrinsic sympathomimetic activity and membrane stabilising activity.

The mechanism of the hypertensive effect has not yet been established. Factors that may be involved include:

- Competitive ability to antagonise catecholamine-induced tachycardia at the beta receptor sites in the heart thus decreasing cardiac output
- Inhibition of renin release by the kidneys
- Inhibition of the vasomotor centres

The exact mechanism by which timolol exercises its antianginal effect is not certain but it may reduce the oxygen requirements of the heart by blocking catecholamine-induced increases in heart rate, systolic blood pressure and the velocity and extent of myocardial contraction. However, oxygen requirements may be increased by such actions as increases in left ventricular fibre length, end diastolic pressure and the systolic ejection period. When the net effect is advantageous in anginal patients it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks. Timolol can therefore increase the capacity for work and exercise in such patients.

Timolol has been found to be effective in prophylactic use for secondary prevention in patients with ischemic heart disease who have survived the acute phase of myocardial infarction. The mechanism of this protective effect is unknown at the present time.

The mechanism of the anti-migraine effect has not been established.

Timolol is also indicated for the treatment of atrial fibrillation.

5.2 Pharmacokinetic properties

Absorption

Timolol is rapidly absorbed from the gastrointestinal tract following oral ingestion (approximately 90%).

Distribution

Detectable plasma levels of timolol occur within 30 minutes, peaking within 1 to 2 hours, and persist for about 8 to 12 hours following oral administration. Timolol is not highly bound to plasma proteins (approximately 10%).

Biotransformation

Timolol is metabolised by the liver, with first pass metabolism converting up to 50% of an orally administered dose. The major metabolites are 1-tert-butylamino-(4-(N-2-hydroxyethylglycolamido)-1,2,5-thiadiazol-3-yloxy)-2-propanol (30%), an ethanolamine derivative (10%) and a lactic acid metabolite (10%).

Elimination

Timolol and its metabolites are eliminated from plasma with a typical half-life of about 4 hours. Renal excretion within a 24-hour period accounted for 68% of a single oral dose, and biliary excretion accounted for about 5% of a single oral dose. Approximately 20% of a single oral dose is excreted in the urine unchanged.

Non-linearity

The individual response to beta adrenoceptor blocking activity varies widely, and no simple correlation exists between the plasma level of timolol and its therapeutic activity. Therefore, objective clinical measurements such as heart rate and/or blood pressure should be used as guides for optimising the dosage for each patient.

5.3 Preclinical safety data

Carcinogenesis

In a two-year study of timolol maleate in rats there was an increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human dose. Similar differences were not observed in rats administered doses equivalent to 25 or 100 times the maximum recommended human dose.

In a life time study in mice there were increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinoma in female mice receiving 500 times the maximum recommended human dose but not at 5 or 50 times the recommended human dose. In a subsequent study in which post-mortem examinations were limited to uterus and lungs, an increase in the incidence of pulmonary tumours was observed at 500 times the recommended human dose.

An increased incidence of mammary adenocarcinoma in rodents has been associated with administration of therapeutic agents which elevate serum prolactin but no correlation between serum prolactin levels and mammary tumours has been established in man. No clinically meaningful changes in serum prolactin have occurred in human female subjects receiving doses of up to 60mg of timolol maleate.

Mutagenesis

Timolol maleate was devoid of mutagenic potential when evaluated in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 times the recommended human dose) and in vivo in a neoplastic cell transformation assay.

Reproductive Studies

Reproduction and fertility studies in rats showed no adverse effect on males or females at doses up to 150 times the recommended human dose.

Teratogenic studies in mice and rabbits at doses up to 50 times the recommended human dose showed no evidence of foetal malformations. Although delayed foetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 times the maximum recommended human dose were maternotoxic in mice and resulted in an increased number of foetal resorptions. Increased foetal resorptions were seen in rabbits at 100 times the maximum recommended human dose but without apparent maternotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-Timol 10mg tablets contain the following inactive ingredients:

- Lactose Monohydrate
- Microcrystalline Cellulose
- Croscarmellose Sodium
- Magnesium Stearate
- Brilliant Blue FCF Al Lake (FD & C Blue No. 1)
- Indigotine Al Lake (FD & C Blue No. 2, indigo carmine)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Shelf life: 3 years from the date of manufacture

6.4 Special precautions for storage

Store at or below 30°C

Protect from heat, light and moisture.

Keep container tightly closed

6.5 Nature and contents of container

APO-Timol 10mg: HDPE bottles containing 100 tablets

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Wairau Valley
AUCKLAND 0627
Telephone: (09) 444 2073
Fax: (09) 444 2951
E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
11 April 1991

10. DATE OF REVISION OF THE TEXT

12 October 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Moved Chemical structure and Molecular formula to section 5.1
3	Change in Pharmaceutical Form – removed “APO” engraving.
4	Minor changes – removed references to drug name to INN name.