PRODUCT INFORMATION

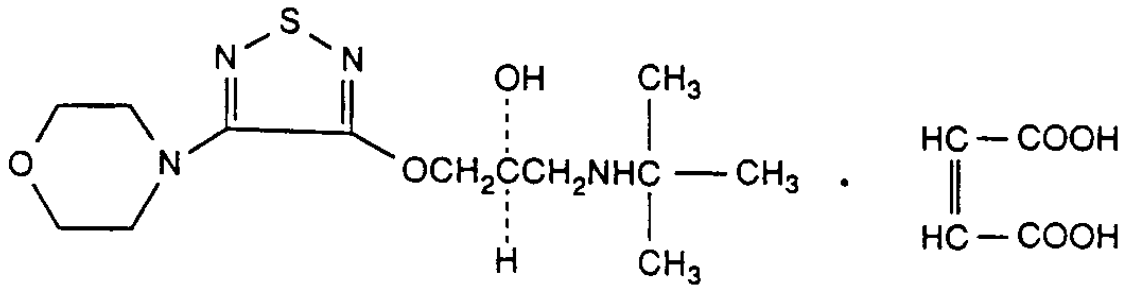
TIMOPTOL-XE®
Sterile Ophthalmic Gellan Solution

NAME OF THE MEDICINE

Timolol maleate

Chemical Structure

Timolol maleate is described chemically as (*S*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom and is provided as the levo isomer. The empirical formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ and the structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odourless, crystalline powder which is soluble in water, methanol, and alcohol.

CAS Number

26921-17-5

DESCRIPTION

TIMOPTOL-XE (timolol maleate) Sterile Ophthalmic Gellan Solution is a formulation of timolol maleate (TIMOPTOL) containing gellan gum.

Gellan gum is a highly purified anionic heteropolysaccharide. Aqueous solutions of gellan gum form a clear transparent gel at low polymer concentrations in the presence of cations. When TIMOPTOL-XE contacts the precorneal tear film, it becomes a gel. The concentration of sodium cation in tears is ideally suited to cause gelation of the material when topically instilled in the conjunctival sac.

Each mL of TIMOPTOL-XE 0.25% contains 2.5 mg of timolol (3.4 mg of timolol maleate). Each mL of TIMOPTOL-XE 0.5% contains 5.0 mg of timolol (6.8 mg of timolol maleate). TIMOPTOL-XE also contains the following inactive ingredients: gellan gum, trometamol,

mannitol and water for injections. Benzododecinium bromide 0.012% is added as the preservative.

PHARMACOLOGY

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol maleate combines reversibly with a part of the cell membrane, the beta-adrenergic receptor, and thus inhibits the usual biologic response that would occur with stimulation of that receptor. This specific competitive antagonism blocks stimulation of the beta-adrenergic receptors by catecholamines having beta-adrenergic stimulating (agonist) activity, whether these originate from an endogenous or exogenous source. Reversal of this blockade can be accomplished by increasing the concentration of the agonist, which will restore the usual biologic response.

TIMOPTOL-XE reduces elevated and normal intraocular pressure whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

Clinical studies have shown that the intraocular pressure lowering effect of TIMOPTOL-XE administered once a day is equivalent to TIMOPTOL administered twice a day. The vehicle of TIMOPTOL-XE, gellan gum, increases the contact time of the drug with the eye.

Maximum reduction of intraocular pressure occurs in two to four hours with TIMOPTOL-XE. Significant lowering of intraocular pressure has been maintained for 24 hours with both 0.25% and 0.5% TIMOPTOL-XE.

TIMOPTOL-XE has a safety profile similar to that of TIMOPTOL, and both are generally well tolerated. In the three studies comparing TIMOPTOL-XE 0.5% once a day to TIMOPTOL 0.5% twice a day, TIMOPTOL-XE did not reduce mean heart rate as much as TIMOPTOL (See PRECAUTIONS). At trough (24 hours post-dose TIMOPTOL-XE, 12 hours post-dose TIMOPTOL), the mean reduction was 0.8 beats/minute for TIMOPTOL-XE and 3.6 beats/minute for TIMOPTOL; whereas at two hours post-dose, the mean reduction in heart rate was comparable (3.8 beats/minute for TIMOPTOL-XE and 5 beats/minute for TIMOPTOL). There was a higher incidence of transient blurred vision following instillation in patients administered TIMOPTOL-XE.

The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established. A fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

In clinical studies timolol maleate was generally effective in more patients and produced fewer and less severe side effects than either pilocarpine or adrenaline (epinephrine).

Unlike miotics, timolol maleate reduces intraocular pressure with little or no effect on accommodation or pupil size. Thus, changes in visual acuity due to increased accommodation are uncommon, and the dim or blurred vision and night blindness produced by miotics are not evident. In addition, in patients with cataracts the inability to see around lenticular opacities when the pupil is constricted by miotics is avoided. When changing

patients from miotics to TIMOPTOL-XE, refraction may be necessary after the effects of the miotic have passed.

As with other antiglaucoma drugs, diminished responsiveness to timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies of TIMOPTOL in which 164 patients were followed for at least 3 years, no significant difference in mean intraocular pressure was observed after initial stabilisation. This indicates that the intraocular pressure-lowering effect of timolol maleate is well maintained.

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function, beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Pharmacokinetics

Following 8 days of once daily application of 0.5% TIMOPTOL-XE in the eye, peak plasma concentrations of timolol averaged <0.3 ng/mL within 4 hours after the last dose. The maximum plasma levels measured approached 0.5 ng/mL at 1 to 2 hours following the last dose.

INDICATIONS

TIMOPTOL-XE is indicated for the reduction of elevated intraocular pressure in patients with:

- ocular hypertension
- chronic open-angle glaucoma
- aphakia and glaucoma

CONTRAINDICATIONS

TIMOPTOL-XE is contraindicated in patients with:

- Reactive airway disease, bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia; sino-atrial block; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock.
- Hypersensitivity to any component of this product.

PRECAUTIONS

As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration (see ADVERSE REACTIONS/Potential Adverse Effects).

Cardio-respiratory Reactions
Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTOL-XE should be discontinued.

Cardiac failure should be adequately controlled before beginning therapy with TIMOPTOL-XE. Patients with a history of cardiovascular disease, including cardiac failure should be watched for signs of deterioration of these diseases, and pulse rates should be monitored.

Due to its negative effect on conduction time, beta-blockers should be given with caution to patients with first degree heart block.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTOL-XE, alternative therapy should be considered.

Respiratory complications, including exacerbation of asthma and death due to bronchospasm in patients with asthma, and cardiac complications, including rarely death in association with cardiac failure, have been reported following administration of beta-adrenergic blocking agents. These are potential complications of therapy with TIMOPTOL-XE.

In patients with mild/moderate chronic obstructive pulmonary disease (COPD), Timoptol XE should be used with caution, and only if the potential benefit outweighs the potential risk.

Muscle weakness
Beta-adrenergic blockage has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis, and generalised weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenic symptoms.

Vascular Disorders
Patients with severe peripheral circulatory disturbance/disorders (e.g. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus
Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who

are receiving insulin or oral hypoglycemic agents. Beta-adrenergic blocking agents may mask the signs and symptoms of acute hypoglycemia.

Masking of Thyrotoxicosis
Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

Surgical Anesthesia
The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists (see ADDITIONAL OVERDOSAGE INFORMATION).

Risk from anaphylactic reaction
While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of adrenaline (epinephrine) used to treat anaphylactic reactions.

Effects on Fertility
Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 100 mg/kg/day.

Use in Pregnancy (Category C)
TIMOPTOL-XE has not been studied in human pregnancy. Beta-adrenergic blocking agents may cause pharmacological effects such as bradycardia in the foetus and newborn infant. During the latter stages of pregnancy and birth, these drugs should be given only after weighing the needs of the mother against the risk to the foetus.

Use in Lactation
Timolol is detectable in human milk. Because of the potential for serious adverse reactions from TIMOPTOL-XE in infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use
Safety and efficacy in children have not been established by adequate and well controlled studies.

Carcinogenicity
In a 2-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day. Similar differences were not observed in rats administered oral doses of 100 mg/kg/day.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, but not at 50 mg/kg/day. In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the

lungs, a statistically significant increase in the incidence of pulmonary tumours was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg, but not at doses of 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumours has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Other

Patients who are already receiving a beta-adrenergic blocking agent orally and who are given TIMOPTOL-XE should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. Timolol maleate has little or no effect on the pupil. Should TIMOPTOL-XE be used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

Choroidal detachment has been reported with the administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

TIMOPTOL-XE has not been studied in patients wearing contact lenses. In a clinical study, the time required to eliminate 50% of the gellan solution from the eye was up to 30 minutes.

Hypersensitivity to any of its ingredients, including the preservative, may develop. Contact irritancy due to the preservative may occur.

Patients should be advised that if they develop an intercurrent ocular condition (e.g. trauma, ocular surgery or infection) or any ocular reactions, particularly conjunctivitis and lid reactions they should immediately seek their physician's advice concerning the continued use of the product.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures. Ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadverstnelty contaimnat by patients who, in most cases, had a concurrent corneal disease or disruption of the ocular epithelial surface.

INTERACTIONS WITH OTHER MEDICINES

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine or another beta-

adrenergic blocking agent, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

The potential exists for hypotension, atrioventricular (AV) conduction disturbances and left ventricular failure to occur in patients receiving a beta-blocking agent when an oral calcium-channel blocker is added to the treatment regimen. The nature of any cardiovascular adverse effect tends to depend on the type of calcium-channel blocker used. Dihydropyridine derivatives, such as nifedipine, may lead to hypotension, whereas verapamil or diltiazem have a greater propensity to lead to AV conduction disturbances or left ventricular failure when used with a beta blocker.

The potential exists for additive effects and production of hypotension and/or marked bradycardia when Timoptol XE is administered together with an oral calcium-channel blockers, catecholamine-depleting drugs, antiarrhythmics, parasympathomimetics or beta-adrenergic blocking agents.

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

Oral calcium-channel antagonists may be used in combination with beta-adrenergic blocking agents when heart function is normal, but should be avoided in patients with impaired cardiac function.

Intravenous calcium-channel blockers should be used with caution in patients receiving beta-adrenergic blocking agents.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine and SSRIs) and timolol.

Although timolol maleate used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with adrenaline (epinephrine) has been reported occasionally. The potential for mydriasis exists from concomitant therapy with TIMOPTOL-XE and adrenaline (epinephrine).

β adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. Caution should be exercised in patients using these drugs concomitantly. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

ADVERSE EFFECTS

TIMOPTOL-XE is usually well tolerated. The most frequent drug-related complaint in the original clinical trials for TIMOPTOL-XE was transient blurred vision (6.0%), lasting from 30 seconds to 5 minutes, following instillation.

In clinical studies, the drug-related adverse experiences observed for TIMOPTOL-XE were similar to those of TIMOPTOL, with the exception of a higher incidence of transient blurred vision for TIMOPTOL-XE (6%) compared to TIMOPTOL (1.6%). Drug-related adverse

experiences caused 3.4% of patients treated with TIMOPTOL-XE to discontinue compared to 1.4% of patients treated with TIMOPTOL. Less than 1% of patients discontinued TIMOPTOL-XE due to transient blurred vision.

The following possibly, probably, or definitely drug-related adverse reactions occurred with frequency of at least 1% in active treatment controlled clinical trials:

Ocular
Common (≥1% and <10%)
Blurred vision, burning and stinging, conjunctival injection, discharge, foreign body sensation, itching.

The following additional adverse reactions have been reported with ocular administration of this or other timolol maleate formulations, either in clinical trials or since the drug has been marketed (also see Potential Adverse Effects).

Special Senses
Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, decreased corneal sensitivity and dry eyes. Visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis, choroidal detachment following filtration surgery (see PRECAUTIONS), tinnitus.

Cardiovascular
Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest, oedema, claudication, Raynaud's phenomenon, cold hands and feet.

Respiratory
Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), exacerbation of asthma, respiratory failure, dyspnoea, cough.

Body as a Whole
Headache, asthenia, fatigue, chest pain.

Integumentary
Alopecia, psoriasiform rash or exacerbation of psoriasis.

Hypersensitivity
Signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash.

Nervous system/Psychiatric
Dizziness, depression, insomnia, nightmares, memory loss, paraesthesia.

Neuromuscular
Increase in signs and symptoms of myasthenia gravis.

Digestive
Nausea, diarrhoea, dyspepsia, dry mouth, abdominal pain.

Urogenital
Decreased libido, Peyronie's disease, sexual dysfunction.

Immunologic
Systemic lupus erythematosus.

Musculoskeletal
Myalgia.

Potential Adverse Effects
The following side effects have been reported in clinical experience with systemic timolol maleate and may be considered potential side effects of ophthalmic timolol maleate.

Body as a Whole
extremity pain, decreased exercise tolerance

Cardiovascular
AV block (2nd or 3rd degree), sinoatrial block, pulmonary oedema, worsening of arterial insufficiency, worsening of angina pectoris, vasodilation

Digestive
vomiting

Endocrine
Hyperglycaemia, hypoglycaemia

Integumentary
Pruritus, sweating, exfoliative dermatitis

Musculoskeletal
arthralgia

Nervous System
Vertigo, local weakness

Psychiatric
Nervousness, diminished concentration, hallucinations, increased dreaming, somnolence

Haematologic
nonthrombocytopenic purpura

Respiratory
rales

Urogenital
Impotence, micturition difficulties

Clinical Laboratory Test findings

Clinically important changes in standard laboratory parameters were rarely associated with the administration of systemic timolol maleate. Slight increases in serum urea, serum

potassium, serum uric acid and triglycerides and slight decreases in haemoglobin, haematocrit, and HDL-cholesterol occurred, but were not progressive or associated with clinical manifestations.

Adverse-Effects, Causal Relationship Unknown

The following adverse effects have been reported but a causal relationship to therapy with timolol maleate has not been established: aphakic cystoid macular oedema, nasal congestion, anorexia, CNS effects (eg., behavioural changes including confusion, anxiety, disorientation and other psychic disturbances), hypertension, retroperitoneal fibrosis, and pseudopemphigoid.

DOSAGE AND ADMINISTRATION

The usual starting dose is one drop of 0.25% TIMOPTOL-XE in the affected eye(s) once a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5% TIMOPTOL-XE in the affected eye(s) once a day. Invert the closed container and shake once energetically before instillation. Depress the bottom of the bottle to dispense one drop.

Dosages higher than one drop of 0.5% TIMOPTOL-XE once a day have not been studied.

If needed, concomitant therapy with other agent(s) for lowering intraocular pressure may be given with TIMOPTOL-XE. Other topically applied medications should be administered no less than 10 minutes before TIMOPTOL-XE. The use of two topical beta-adrenergic blocking agents is not recommended (see PRECAUTIONS).

Systemic absorption of drugs from ophthalmic solutions may be minimised by pressure on the tear-duct immediately after application. This may result in an increase in local activity.

HOW TO TRANSFER PATIENTS FROM OTHER THERAPY

When a patient is transferred from TIMOPTOL to TIMOPTOL-XE, TIMOPTOL should be discontinued after proper dosing on one day, and treatment with the same concentration of TIMOPTOL-XE started on the following day.

When a patient is transferred from another topical ophthalmic beta-adrenergic blocking agent, that agent should be discontinued after proper dosing on one day and treatment with TIMOPTOL-XE started on the following day with 1 drop of 0.25% TIMOPTOL-XE in the affected eye once a day. The dose may be increased to one drop of 0.5% TIMOPTOL-XE once a day if the clinical response is not adequate.

When a patient is transferred from a single antiglaucoma agent, other than a topical ophthalmic beta-adrenergic blocking agent, continue the agent and add one drop of 0.25% TIMOPTOL-XE to each affected eye once a day. On the following day, discontinue the previously used antiglaucoma agent and continue TIMOPTOL-XE. If a greater response is required, substitute one drop of 0.5% TIMOPTOL-XE for the 0.25% dosage.

OVERDOSAGE

There have been reports of inadvertent overdosage with TIMOPTOL resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Contact the Poisons Information Centre on 131126 for advice on management.

The following specific therapeutic measures should be considered:

(1) Symptomatic bradycardia: Administer atropine sulphate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoprenaline hydrochloride should be administered cautiously. In refractory cases the use of a transvenous cardiac pacemaker may be considered.

(2) Heart block (second or third degree): Administer isoprenaline hydrochloride or insert a transvenous cardiac pacemaker.

(3) Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or noradrenaline. In refractory cases the use of glucagon hydrochloride has been reported to be useful.

(4) Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride, which has been reported to be useful.

(5) Bronchospasm: Administer isoprenaline hydrochloride. Additional therapy with aminophylline may be considered.

Timolol does not dialyse readily.

PRESENTATION AND STORAGE CONDITIONS

TIMOPTOL-XE is a sterile, colourless to nearly colourless, slightly opalescent, slightly viscous, aqueous ophthalmic solution.

TIMOPTOL-XE 2.5 mg/mL: 2.5 mL bottle with a controlled dropper tip and white cap. Store at or below 25°C. Avoid freezing. Protect from light. Discard within 28 days of opening.

TIMOPTOL-XE 5.0 mg/mL: 2.5 mL bottle with a controlled dropper tip and white cap. Store at or below 25°C. Avoid freezing. Protect from light. Discard within 28 days of opening.

NAME AND ADDRESS OF THE SPONSOR

Mundipharma Pty Limited
ABN 87 081 322 509
88 Phillip Street

Sydney NSW 2000

Further information may be obtained from Mundipharma's Medical Information Department 1800 188 009.

POISON SCHEDULE OF THE MEDICINE

(S4) Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29 July 1999

DATE OF MOST RECENT AMENDMENT

20 April 2017

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