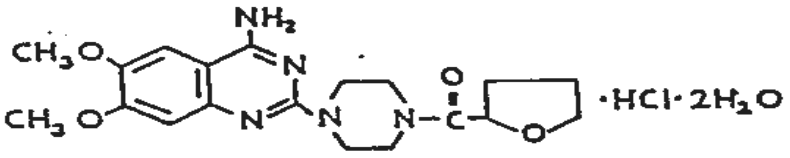
PRODUCT INFORMATION

HYTRIN™

NAME OF THE MEDICINE

Terazosin hydrochloride

Terazosin hydrochloride, an alpha-1-selective adrenoceptor blocking agent, is a quinazoline derivative represented by the following chemical name:
1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl) carbonyl]-Piperazine, monohydrochloride, dihydrate.
The empirical formula is $C_{19}H_{25}N_5O_4.HCl•2H_2O$ and its structural formula is:



Terazosin hydrochloride is a white, crystalline substance, freely soluble in water and isotonic saline and has a molecular weight of 459.93.

DESCRIPTION

Hytrin tablets for oral ingestion are supplied in four dosage strengths containing terazosin hydrochloride dihydrate equivalent to 1 mg, 2 mg, 5 mg, and 10 mg terazosin. Each tablet also contains as excipients lactose, maize starch, pregelatinised maize starch, purified talc and magnesium stearate. Hytrin 2mg tablets also contain quinoline yellow Al, 5mg tablets contain iron oxide red, iron oxide yellow and iron oxide black and 10mg tablets contain indigo carmine Al lake as colourants.

PHARMACOLOGY

Pharmacodynamics

In animals, terazosin causes a decrease in blood pressure by decreasing total peripheral vascular resistance. The vasodilatory hypotensive action of terazosin appears to be produced mainly by blockade of alpha-1-adrenoceptors. Terazosin decreases blood pressure gradually within 15 minutes following oral administration.

In man, systolic and diastolic blood pressures are lowered in both the supine and standing positions. The effect is most pronounced on the diastolic blood pressure. These changes are usually not accompanied by reflex tachycardia. A greater blood pressure effect associated with peak plasma concentrations (first few hours after dosing) appears somewhat more position-dependent (greater in the erect position) than the effect of terazosin at 24 hours, and in the erect position there is also a 6-10 beat per minute increase in heart rate in the first few hours after dosing.

Studies suggest that alpha-1-adrenoceptor blockade is also useful in improving the urodynamics in patients with chronic bladder outlet obstruction, such as in benign prostatic hyperplasia (BPH).

The symptoms of BPH are caused mainly by the presence of an enlarged prostate and by the increased smooth muscle tone of the bladder outlet and the prostate, which is regulated by alpha-1-adrenergic receptors.

In *in vitro* experiments, terazosin has been shown to antagonise phenylephrine-induced contractions in human prostatic tissue. In clinical trials terazosin has been shown to improve the urodynamics and symptomatology in patients with BPH.
There is a tendency for patients to gain weight during terazosin therapy. In placebo-controlled monotherapy trials, male and female patients receiving terazosin gained a mean of 0.8 and 1 kg (1.7 and 2.2 pounds) respectively, compared to losses of 0.1 and 0.5 kg (0.2 and 1.2 pounds) respectively, in the placebo group. Both differences were significant.

During controlled clinical studies, patients receiving terazosin had an improved lipid profile. Patients receiving terazosin monotherapy had a small but statistically significant decrease compared to placebo in total cholesterol and the combined low-density and very-low-density lipoprotein fractions. These patients had significant increases from baseline in high-density lipoproteins, the HDL/LDL cholesterol ratio, and significant decreases from baseline in triglycerides. However, these changes were not significant when compared to placebo.

Long-term (6 months or longer) administration of terazosin has produced no pattern of clinically significant changes attributable to the drug in the following clinical laboratory measurements: Glucose, uric acid, creatinine, BUN, liver function tests, and electrolytes. Analysis of clinical laboratory data following administration of terazosin suggested the possibility of haemodilution based on decreases in haematocrit, haemoglobin, white blood cells, total protein, and albumin. Decreases in haematocrit and total protein have been observed with alpha-blockade and are attributed to haemodilution.

Pharmacokinetics

Relative to solution, terazosin hydrochloride administered as terazosin tablets is essentially completely absorbed in man. Terazosin has been shown to undergo minimal hepatic first-pass metabolism and nearly all of the circulating dose is in the form of parent drug. The plasma levels peak about one hour after dosing, and then decline with a half-life of approximately 12 hours. The drug is highly bound to plasma proteins and binding is constant over the clinically observed concentration range. Approximately 10% of an orally administered dose is excreted as parent drug in the urine and approximately 20% is excreted in the faeces. The remainder is eliminated as metabolites. Overall, approximately 40% of the administered dose is excreted in the urine and approximately 60% in the faeces. The disposition of the compound in animals is qualitatively similar to that in man.

The pharmacokinetics of terazosin appear to be independent of renal function. This would obviate the need to adjust dosing regimens for patients with impaired renal function.

INDICATIONS

Hytrin (terazosin hydrochloride) is indicated for the relief of the manifestations of mild to moderate benign prostatic hyperplasia (BPH). Treatment should be stopped if patients have not responded after three months of therapy.

Terazosin is also indicated in the treatment of hypertension. It can be used alone or in combination with other antihypertensive agents such as diuretics or beta-adrenergic blocking agents.

CONTRAINDICATIONS

Terazosin is contraindicated in patients known to be hypersensitive to terazosin hydrochloride or its analogues.

PRECAUTIONS

Syncope and "First-dose" Effect

May occur when used in both hypertension and BPH.

Terazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially postural hypotension, and syncope in association with the first dose or first few doses of therapy. A similar effect can be anticipated if therapy is interrupted for more than a few doses. Syncope has also been reported with other alpha-adrenergic blocking agents in association with rapid dosage increases or the introduction of another antihypertensive drug. Syncope is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120-160 beats per minute.

To decrease the likelihood of syncope or excessive hypotension, treatment should always be initiated with a 1 mg dose of terazosin, given at bedtime. The 2 mg, 5 mg, and 10 mg tablets are not indicated as initial therapy. Dosage should then be increased slowly, according to recommendations in the Dosage and Administration section and additional antihypertensive agents should be added with caution. The patient should be cautioned to avoid situations where injury could result should syncope occur during initiation of therapy.

In multiple dose clinical trials involving nearly 2000 patients, syncope was reported in about 1% of patients, in no case severe or prolonged, and was not necessarily associated with early doses. In clinical studies involving treatment of approximately 1200 patients with BPH, the incidence of syncope was 0.7%.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary. There is evidence that the orthostatic effect of terazosin is greater, even in chronic use, shortly after dosing.

Orthostatic Hypotension

While syncope is the most severe orthostatic effect of terazosin, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, and palpitations, are more common. Patients with occupations in which such events represent potential problems should be treated with particular caution.

Information for Patients

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and to avoid driving or hazardous tasks for 12 hours after the first dose, after dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of terazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered.

Patients should also be told that drowsiness or somnolence can occur with terazosin, requiring caution in people who must drive or operate heavy machinery.

Cataract Surgery

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients on/or previously treated with alpha-1 blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker therapy prior to cataract surgery.

Effects on Fertility

The effect of terazosin on fertility was assessed in a standard fertility/ reproductive performance study in which male and female rats were administered oral doses of 8, 30, and 120 mg/kg/day. Four of 20 male rats given 30 mg/kg and five of 19 male rats given 120 mg/kg failed to sire a litter. Testicular weights and morphology were unaffected by treatment. Vaginal smears at 30 and 120 mg/kg/day, however, appeared to contain less sperm than smears from control matings and good correlation was reported between sperm count and subsequent pregnancy.

Oral administration of terazosin for one or two years elicited a statistically significant increase in the incidence of testicular atrophy in rats exposed to 40 and 250 mg/kg/ day, but not in rats exposed to 8 mg/kg/day (greater than 20 times the maximum recommended human dose). Testicular atrophy was also observed in dogs dosed with 300 mg/kg/day (greater than 800 times the maximum recommended human dose) for three months but not after one year when dosed with 20 mg/kg/day. This lesion has also been seen with prazosin, another selective alpha-1 blocking agent. As human investigation has not been carried out, the relevance of this finding to man is not known.

Use In Pregnancy

Teratogenic effects: Pregnancy Category B2. Terazosin was not teratogenic in either rats or rabbits when administered in oral doses up to 1330 and 165 times, respectively, the maximum recommended human dose. Foetal resorptions occurred in rats dosed with 480 mg/kg/day, approximately 1330 times the maximum recommended human dose. Increased foetal resorptions, decreased foetal weight and an increased number of supernumerary ribs were observed in offspring of rabbits dosed with 165 times the maximum recommended human dose. These findings (in both species) were most likely secondary to maternal toxicity. There are no adequate and well-controlled studies in pregnant women and the safety of terazosin in pregnancy has not been established. Terazosin is not recommended during pregnancy unless the potential benefit justifies the potential risk to the mother and foetus.

Nonteratogenic effects: In a peri- and post-natal development study in rats, significantly more pups died in the group dosed with 120 mg/kg/day (greater than 300 times the maximum recommended human dose) than in the control group during the three-week postpartum period.

Use in Lactation

It is not known whether terazosin is excreted in breast milk. Because many drugs are excreted in breast milk, caution should be exercised when terazosin is administered to a nursing woman.

Paediatric Use

Safety and effectiveness in children have not been determined.

Carcinogenicity

Terazosin was devoid of mutagenic potential when evaluated *in vivo* and *in vitro* (the Ames test, *in vivo* cytogenetics, the dominant lethal test in mice, *in vivo* Chinese hamster chromosome aberration test and V79 forward mutation assay).

Terazosin, administered in the feed to rats at a dosage of 8, 40, and 250 mg/kg/day for two years, was associated with a statistically significant increase in benign adrenal medullary tumours in male rats exposed to the 250 mg/kg dose. This dose is 695 times the maximum recommended human dose of 20 mg/55 kg patient. Female rats were unaffected. Terazosin was not oncogenic in mice when administered in feed for 2 years at a maximum tolerated dose of 32 mg/kg/day.

Genotoxicity

The absence of mutagenicity in a battery of tests, of tumourigenicity of any cell type in the mouse carcinogenicity assay, of increased total tumour incidence in either species, and of proliferative adrenal lesions in female rats suggests a male rat species-specific event. Numerous other diverse pharmaceutical and chemical compounds have also been associated with benign adrenal medullary tumours in male rats without supporting evidence for carcinogenicity in man.

Interactions with other Medicines

Hypertension

In controlled trials, terazosin has been added to diuretics, and several beta-adrenergic blockers; no unexpected interactions were observed. Terazosin has also been used in patients on a variety of concomitant therapies; while these were not formal interaction studies, no interactions were observed. Terazosin has been used concomitantly in at least 50 patients on the following drugs or drug classes:

1. analgesic/anti-inflammatory (e.g. paracetamol, aspirin, codeine, ibuprofen, indomethacin)
2. antibiotics (e.g. erythromycin, trimethoprim, sulphamethoxazole)
3. anticholinergic/sympathomimetics (e.g. phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride)
4. antigout (e.g. allopurinol)
5. antihistamines (e.g. chlorpheniramine)
6. cardiovascular agents (e.g. atenolol, hydrochlorothiazide, methyclothiazide, propranolol)
7. corticosteroids
8. gastrointestinal agents (e.g. antacids)
9. hypoglycaemics
10. sedatives and tranquillizers (e.g. diazepam).

Benign Prostatic Hyperplasia (BPH)

In clinical trials in BPH patients the number reporting dizziness or other dizziness-related adverse events appears to be greater in those patients receiving terazosin and ACE inhibitors or diuretics and the number reporting asthenia was greater in those receiving terazosin and NSAID, than in the total

population of terazosin patients from double-blind, placebo-controlled studies. No interactions were observed in patients treated concurrently with theophylline, anti-anginal agents or oral hypoglycaemic agents.

PDE-5 Inhibitors

Hypotension has been reported when terazosin has been used with phosphodiesterase-5 (PDE-5) inhibitors

ADVERSE EFFECTS

Hypertension

The prevalence of adverse reactions has been ascertained from clinical studies conducted primarily in the United States. All adverse experiences (events) reported during these studies were recorded as adverse reactions. The prevalence rates presented below are based on combined data from 14 placebo-controlled studies involving once-a-day administration of terazosin as monotherapy or in combination with other antihypertensive agents, at doses ranging from 1 to 40 mg. Table 1 summarizes those adverse experiences reported for patients in these studies where the prevalence rate for the terazosin group was at least 5%, where the prevalence rate for the terazosin group was at least 2% and was greater than the prevalence rate for the placebo group, or where the reaction is of particular interest.

Asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral oedema, palpitations, and somnolence were the only symptoms that were significantly (p less than 0.05) more common in patients receiving terazosin than in patients receiving placebo. Similar adverse reaction rates were observed in placebo-controlled monotherapy trials as in combination therapy trials. (See Table 1)

Table 1 Adverse Reactions During Placebo-Controlled Studies In Hypertension

	Terazosin (N=859)	Placebo (N=506)
BODY AS A WHOLE		
Asthenia +	11.3% *	4.3%
Back Pain	2.4%	1.2%
Headache	16.2%	15.8%
CARDIOVASCULAR SYSTEM		
Palpitations	4.3% *	1.2%
Postural Hypotension	1.3%	0.4%
Tachycardia	1.9%	1.2%
DIGESTIVE SYSTEM		
Nausea	4.4% *	1.4%
METABOLIC/NUTRITIONAL DISORDERS		
Oedema	0.9%	0.6%
Peripheral Oedema	5.5% *	2.4%
Weight Gain	0.5%	0.2%
MUSCULOSKELETAL SYSTEM		
Pain-Extremities	3.5%	3.0%
NERVOUS SYSTEM		
Depression	0.3%	0.2%
Dizziness	19.3% *	7.5%
Libido Decreased	0.6%	0.2%

Nervousness	2.3%	1.8%
Paraesthesia	2.9%	1.4%
Somnolence	5.4%	2.6%
RESPIRATORY SYSTEM		
Dyspnea	3.1%	2.4%
Nasal Congestion	5.9% *	3.4%
Sinusitis	2.6%	1.4%
SPECIAL SENSES		
Blurred Vision	1.6% *	0.0%
UROGENITAL SYSTEM		
Impotence	1.2%	1.4%

+ Includes weakness, tiredness, lassitude and fatigue.
* Statistically significant at p = 0.05 level.

The adverse reactions were usually mild or moderate in intensity, but sometimes were serious enough to interrupt treatment. The adverse reactions that were most bothersome, as judged by their being reported as reasons for discontinuation of therapy by at least 0.5% of the terazosin group and being reported more often than in the placebo group, are shown in Table 2. Overall, 9.9% of 859 patients taking terazosin discontinued therapy because of adverse effects, as compared with 4.2% of 506 patients taking placebo.

Table 2 Discontinuations During Placebo-Controlled Studies In Hypertension

	Terazosin (N=859)	Placebo (N=506)
BODY AS A WHOLE		
Asthenia	1.6%	0.0%
Headache	1.3%	1.0%
CARDIOVASCULAR SYSTEM		
Palpitations	1.4%	0.2%
Postural Hypotension	0.5%	0.0%
Syncope	0.5%	0.2%
Tachycardia	0.6%	0.0%
DIGESTIVE SYSTEM		
Nausea	0.8%	0.0%
METABOLIC/NUTRITONAL DISORDERS		
Peripheral Oedema	0.6%	0.0%
NERVOUS SYSTEM		
Dizziness	3.1%	0.4%
Paraesthesia	0.8%	0.2%
Somnolence	0.6%	0.2%
RESPIRATORY SYSTEM		
Dyspnea	0.9%	0.6%
Nasal Congestion	0.6%	0.0%

SPECIAL SENSES		
Blurred Vision	0.6%	0.0%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to terazosin. The following additional adverse reactions were reported by at least 1% of 1987 patients who received terazosin in controlled or open, short- or long-term clinical studies or have been reported during marketing experience:

Body as a whole: chest pain, facial oedema, fever, abdominal pain, neck pain, shoulder pain.

Cardiovascular System: arrhythmia, vasodilation

Digestive System: constipation, diarrhoea, dry mouth, dyspepsia, flatulence, vomiting.

Metabolic/Nutritional Disorders: gout

Musculoskeletal System: arthralgia, arthritis, joint disorder, myalgia

Nervous System: anxiety, insomnia

Respiratory System: bronchitis, cold symptoms, epistaxis, flu symptoms, increased cough, pharyngitis, rhinitis

Skin and Appendages: pruritus, rash, sweating

Special Senses: abnormal vision, conjunctivitis, tinnitus

Urogenital System: urinary frequency, urinary tract infection.

At least two cases of severe anaphylactoid reactions were reported to be associated with administration of terazosin hydrochloride.

Benign Prostatic Hyperplasia (BPH)

Each selected adverse event in Table 3 was chosen on the basis of meeting one or more of the following criteria:

1) Incidence of ≥ 5% or clinical relevance in previous terazosin hypertension clinical studies;

2) Incidence ≥ 5% in terazosin BPH clinical studies;

3) It was a component of the dizziness-related adverse event complex, which includes dizziness, hypotension, postural hypotension, syncope and vertigo; or

4) It was related to sexual function.

Table 3 Summary Of Selected Adverse Events From Six Double-Blind, Placebo-Controlled Studies In Benign Prostatic Hyperplasia (Bph)

	Terazosin (N= 636)	Placebo (N = 360)
BODY AS A WHOLE		
Asthenia	7.4%*	3.3%
Headache	4.9%	5.8%
CARDIOVASCULAR SYSTEM		
Hypotension	0.6%	0.6%
Palpitation	0.9%	1.1%
Postural Hypotension	3.9%*	0.8%
Syncope	0.6%	0.0%
Tachycardia	0.3%	0.0%
DIGESTIVE SYSTEM		
Nausea	1.7%	1.1%
METABOLIC/NUTRITIONAL DISORDERS		
Peripheral Oedema	0.9%	0.3%
Weight Gain	0.5%	0.0%
NERVOUS SYSTEM		
Dizziness	9.1%*	4.2%
Libido Decreased	0.9%	0.3%
Somnolence	3.6%*	1.9%
Vertigo	1.4%	0.3%
RESPIRATORY SYSTEM		
Dyspnea	1.7%	0.8%
Nasal Congestion/Rhinitis	1.9%*	0.0%
SPECIAL SENSES		
Blurred Vision/Amblyopia	1.3%	0.6%
UROGENITAL SYSTEM		
Impotence	1.6%*	0.6%

* $P \leq 0.05$ compared to placebo group

Laboratory Tests: Small but statistically significant decreases in haematocrit, haemoglobin, white blood cells, total protein and albumin were observed in controlled clinical trials. The magnitude of the decreases did not worsen with time.

Post-Marketing Experience
Thrombocytopenia has been reported. Atrial fibrillation has been reported. Priapism has been reported. Anaphylaxis has been reported. Angioedema has been reported. Hypersensitivity has been reported.

During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha-1 blocker therapy (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

The dose of terazosin should be adjusted according to the patient's individual response. The following is a guide to its administration:

Initial Dose

1 mg at bedtime is the starting dose for all patients, and this dose should not be exceeded. This initial dosing regimen should be strictly observed to minimize the potential for severe hypotensive effects.

Subsequent Doses

Benign Prostatic Hyperplasia (BPH)

The dose may be slowly increased to achieve the desired clinical response in BPH patients. The usual recommended dose range is 5 to 10 mg administered once a day. Treatment should commence with one tablet of 1 mg taken at bedtime for the first 4 days, then every morning for the next 3 days. For the next seven days, the dosage is one tablet of 2 mg every morning. In the third week, the dosage is increased to one tablet of 5 mg every morning. As from the fourth week, a maintenance dosage of 5-10 mg is taken daily each morning.

Urine flow rate measured approximately 24 hours after the last dose has shown that the beneficial effect in BPH persists for the recommended dosing interval. Symptom improvements have been detected as early as two weeks after starting treatment with terazosin. Improvements in flow rate may be seen somewhat later.

Maximal benefit appears to occur after 3 to 6 months of treatment, but it appears that there is little to be gained by continuing treatment for more than 6 months if there has been no clinical response. Efficacy has been demonstrated in clinical studies of up to 18 months but data on longer term use is not yet available. If terazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen.

Hypertension

The dose may be slowly increased to achieve the desired blood pressure response. The usual recommended dose range is 1 mg to 5 mg administered once a day; however, some patients may benefit from doses as high as 20 mg per day. Doses over 20 mg do not appear to provide further blood pressure effect and doses over 40 mg have not been studied. Blood pressure should be monitored at the end of the dosing interval to be sure control is maintained throughout the interval. It may also be helpful to measure blood pressure 2-3 hours after dosing to see if the maximum and minimum responses are similar, and to evaluate symptoms such as dizziness or palpitations which can result from excessive hypotensive response. If the response is substantially diminished at 24 hours, an increased dose or use of a twice daily regimen can be considered. If terazosin administration is discontinued for several days or longer, therapy should be reinstituted using the initial dosing regimen. In clinical trials, except for the initial dose, the dose was given in the morning.

Use with Other Drugs

Caution should be observed when terazosin is administered concomitantly with other antihypertensive agents (e.g. calcium antagonists) to avoid the possibility of significant hypotension. When adding a diuretic or other antihypertensive agent, dosage reduction and retitration may be necessary. (See "drug interactions")

There are no data available concerning the use of terazosin in combination with other agents used for treating benign prostatic hyperplasia, eg finasteride.

OVERDOSAGE

Should overdosage of terazosin lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed.

Laboratory data indicate that terazosin is highly protein bound; therefore, dialysis may not be of benefit.

For advice on the management of overdose please contact the Poisons Information Centre, phone 131126.

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C

Round, flat bevelled edge tablets, embossed with Abbott logo, available in the following strengths;

HYTRIN 1mg: White tablet
HYTRIN 2mg: Yellow tablet
HYTRIN 5mg: Tan tablet
HYTRIN 10mg: Blue tablet

HYTRIN Starter Pack contains 7 x 1mg tablets and 7 x 2mg tablets in a blister pack

HYTRIN 2mg tablets, 5mg tablets and 10mg tablets are presented in blister packs of 28 tablets

NAME AND ADDRESS OF THE SPONSOR

BGP Products Pty Ltd
299 Lane Cove Rd
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

17 October 2005

DATE OF MOST RECENT AMENDMENT

2 July 2015

Version 9