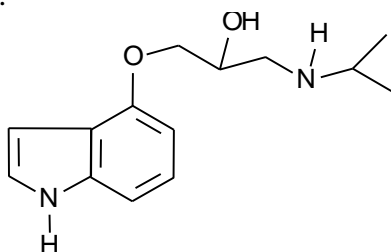


VISKEN[®]

pindolol

NAME OF THE MEDICINE

Active ingredient:	Pindolol
Chemical name:	(±)-4-(2-hydroxy-3-isopropylaminopropoxy)-indole
CAS number:	13523-86-9
Molecular weight:	248.33
Molecular formula:	C ₁₄ H ₂₀ N ₂ O ₂
Molecular weight:	248.33
Chemical structure:	



DESCRIPTION

Pindolol is a weak base (pK_a 9.2), slightly soluble in water (< 0.1 % w/v at neutral pH) and readily soluble in acidic, aqueous buffers. Solubility in ethanol (95 % v/v) is 0.62 %.

Visken tablets contain pindolol, colloidal anhydrous silica, magnesium stearate, pregelatinised maize starch, and microcrystalline cellulose.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: beta-adrenergic blocking agents; beta blockers

ATC code: C07AA03

Visken is a competitive non-selective beta-adrenoreceptor antagonist with intrinsic sympathomimetic activity but insignificant membrane stabilising activity.

In patients with excessive sympathetic nervous activity Visken reduces heart rate, force of cardiac contraction and cardiac output leading to reduced oxygen demand of the myocardium.

In hypertensive patients, a single oral administration of Visken may reduce blood pressure, heart rate and cardiac output but under chronic administration cardiac output returns to pre-treatment levels while systemic vascular resistance is reduced; blood pressure remains lowered.

Plasma renin activity is reduced by both single doses and chronic administration of Visken.

In addition to its beta-adrenoceptor antagonist activity Visken also exhibits intrinsic sympathomimetic activity (ISA). The full significance of the various clinical manifestations of this partial agonist activity is not yet established.

Pharmacokinetics

Absorption:

Studies in fasting normal subjects indicate that Visken is completely absorbed from the small intestine, with peak plasma concentrations being recorded between 1 and 2 hours after oral ingestion. It is highly bioavailable since it is not subject to significant first pass elimination by the liver. The peak plasma level after a single oral dose is directly proportional to dosage over the therapeutic range and there is only a two to three- fold intersubject variation. Consequently establishment of therapeutic blood levels is rapid. Food taken immediately after administration of the drug does not alter significantly the extent or rate of absorption.

Distribution:

The available data relates to tissue distribution of radioactivity following intravenous administration of ¹⁴C-pindolol to rats. Immediately following initial distribution (0.5 h) the level of radioactivity in virtually all tissues is greater than in blood (particularly liver, kidneys, lungs, salivary glands and small intestine). After 2 hours many tissues, including brain, have comparable or lower levels of radioactivity than does blood. Low but significant levels, probably of slowly excreted metabolites, reside in liver, adrenals, skin, thyroid and kidneys at 24 hours. The volume of distribution is 2 L to 3 L per kg.

In human plasma, Visken is approximately 40 % bound to plasma proteins; the degree of binding is independent of concentration.

It may be anticipated that Visken will cross the placental barrier.

Metabolism:

In man approximately 60% of the drug is metabolised, mainly by conjugation. There are no known active metabolites.

Elimination:

Over 90 % of the drug is excreted by the kidney, approximately 40 % unchanged. The half-life of elimination of pindolol averages 3.3 hours.

Food effect:

No significant differences in absorption of pindolol were observed with or without food.

Characteristics in special populations:Patients with hepatic / renal impairment:

Patients with impaired renal or hepatic function may usually be treated with normal doses. Only severe cases may require a reduction of the daily dose.

Elderly patients:

The elderly population may show higher plasma concentrations of pindolol as a combined result of a decreased metabolism of the drug in elderly population, a decreased hepatic blood flow and a decreased renal elimination.

Pregnancy:

The elimination half-life of pindolol does not differ significantly between pregnant and non-pregnant patients (see PRECAUTIONS).

CLINICAL TRIALS

Pindolol is an established medicine.

INDICATIONS

- Hypertension (monotherapy or in combination with other antihypertensive drugs)
- Angina pectoris (prevention of attacks)
- Cardiac arrhythmias [sinus tachycardia, paroxysmal tachycardia, supraventricular and ventricular extrasystoles, drug induced extrasystoles (digitalis), atrial flutter and fibrillation - to slow the ventricular rate].
- Functional hyperadrenergic cardiac disturbances (hyperkinetic heart syndrome, neurocirculatory asthenia).

CONTRAINDICATIONS

- 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.

- Allergic disorders (including allergic rhinitis) which may suggest a predisposition to bronchospasm
- Right ventricular failure secondary to pulmonary hypertension
- Cor pulmonale
- Sinus bradycardia (less than 45-50 beats/minute)
- Sick sinus syndrome
- Second and third degree A-V block
- Shock (including cardiogenic and hypovolemic shock)
- Hypersensitivity to pindolol, any of the excipients, or cross-sensitivity to other beta blockers
- Decompensated cardiac failure
- Prinzmetal's angina (variant angina)
- Severe peripheral arterial circulatory disturbances
- Untreated pheochromocytoma
- History of bronchospasm
- Bronchial asthma
- Chronic obstructive lung disease

PRECAUTIONS

Cardiovascular system

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, the beta-blocker should be withdrawn.

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.

Although pindolol produces less depression of resting myocardial function than beta-blockers without intrinsic sympathomimetic activity (ISA), patients with incipient or manifested heart failure must be adequately compensated before treatment with Visken. Similarly, if Visken is used for the treatment of acute myocardial infarction, it is necessary to monitor cardiovascular parameters closely.

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 8-14 days during which time the patient's progress should be assessed. The drug may be reinstated 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.

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. Owing to the danger of cardiac arrest, a calcium channel blocker of the verapamil type must not be administered intravenously to a patient already receiving treatment with a beta-blocker.

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.

See INTERACTIONS WITH OTHER MEDICINES.

Psoriasis

Since beta-blockers may aggravate psoriasis, pindolol should only be prescribed after careful consideration of benefits and risks in patients with history of psoriasis.

Oculomuocutaneous Syndrome

The full development of oculomuocutaneous syndrome, as previously described with practolol, has not yet been reported with pindolol. However, some features of this syndrome have been noted such as dry eyes and skin rash. In most cases the symptoms cleared after withdrawal of treatment. Discontinuation of pindolol should be considered and switch to another therapeutic agent might be advisable.

Peripheral Vascular Disease

Beta-blockade may impair the peripheral circulation and exacerbate the symptoms of peripheral vascular disease. However, because of its sympathomimetic effects mediated at the vascular β_2 -receptors (vasodilatation), peripheral vascular side effects (cold extremities) are only rarely encountered during pindolol therapy.

Antiarrhythmic Drugs

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

Prinzmetal Angina

There is a risk of exacerbating coronary artery spasm in 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.

Euthyroid Hyperthyroxinaemia

The effects of beta-blockers on thyroid hormone metabolism may result in elevations of serum free thyroxine (T₄) levels. In the absence of any signs or symptoms of hyperthyroidism, additional investigation is necessary before a diagnosis of thyrotoxicosis can be made.

Anaesthesia and the Peri-operative Period

It is essential to monitor cardiovascular function closely during general anaesthesia in patients treated with a beta-blocker.

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.

See INTERACTIONS WITH OTHER MEDICINES.

Anaphylactic Reaction

Visken is less likely to cause a rebound super sensitivity to beta-adrenoceptor stimulation following abrupt cessation of chronic therapy than are beta-blockers without ISA. However, if interruption of therapy is considered necessary, it is advisable to reduce the dose of Visken progressively.

Anaphylactic reactions precipitated by other agents may be particularly severe in patients taking beta-blockers, especially non-selective beta-blockers, and may be resistant to normal doses of adrenaline. Whenever possible, beta-blockers should be avoided in patients who are at increased risk for anaphylaxis.

Diabetes

Diabetic patients, especially those dependant on insulin, should be warned that beta-blockers affect glucose metabolism, and may mask some important premonitory signs of acute hypoglycaemia (e.g. palpitations, tachycardia, and tremor), whereas sweating is not inhibited. 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 concurrent use of beta-blockers and antidiabetic medication should always be monitored to confirm that diabetic control is well maintained. The dose of insulin or oral hypoglycaemic agent may need adjustment.

See INTERACTIONS WITH OTHER MEDICINES.

Other Metabolic Effects

Beta-adrenoceptors 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.

Renal Function

In patients with severe renal impairment, 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.

Use of Catecholamine-depleting Agents

Concomitant use of drugs such reserpine and guanethidine requires careful monitoring since the added effect of beta-blockade may produce an excessive reduction of the resting sympathetic nervous tone. See INTERACTIONS WITH OTHER MEDICINES.

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. See INTERACTIONS WITH OTHER MEDICINES.

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.

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.

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.

Hyperthyroidism

Because beta-blockers may mask the clinical signs of developing or continuing hyperthyroidism (e.g. tachycardia), resulting in symptomatic improvement without any change in thyroid hormone status, special care should be exercised in patients who are hyperthyroid and are also receiving beta-blockers. These patients should be carefully monitored for thyroid function.

Use in Pregnancy (Category C)

Beta-blockers may cause bradycardia in the foetus and newborn infant. During the later stages of pregnancy these drugs should only be given after weighing the needs of the mother against the risk to the foetus.

Experimental studies in animals with pindolol give no evidence of teratogenicity. However the effects on the human foetus and pregnant uterus are not yet fully known and Visken should only be administered under compelling circumstances.

Use in Lactation

Visken can pass in minute quantities into breast milk but there is no evidence that it affects the infant. Nevertheless, the drug should not be given to lactating women unless the expected benefit outweighs the potential risk.

Use in Children

At the present time the data on the use of Visken in children are too limited to recommend its use.

Use in the Elderly

Geriatric patients should be treated cautiously. An excessive decrease in blood pressure or pulse rate may reduce blood supply to vital organs to inadequate levels.

Effect on Ability to Drive and Use Machines

Because dizziness or fatigue may occur during initiation of treatment with beta-adrenoceptor blocking drugs, patients driving a vehicle or operating machinery should exercise caution until they have determined their individual reaction to treatment.

INTERACTIONS WITH OTHER MEDICINES**Anticipated interactions resulting in concomitant use not being recommended****Monoamine Oxidase (MAO) 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.

Anticipated interactions to be considered**Antidiabetic agents:**

Beta-blockers may interfere with the usual hemodynamic response to hypoglycaemia and produce a rise in blood pressure associated with severe bradycardia. Although the clinical importance of these effects with pindolol is probably small in most diabetic

patients, but beta-blockers should be avoided in unstable diabetic patients prone to episodes of hypoglycaemia (see PRECAUTIONS).

Calcium-channel blocking agents:

Experience has shown that 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. Oral treatment requires careful monitoring, especially when the beta-blocker is combined with a verapamil-type calcium antagonist.

The possibility of severe reduction in blood pressure upon the concomitant administration of dihydropyridine derivatives such as nifedipine with pindolol in patients with latent cardiac insufficiency cannot be excluded.

Anti-adrenergic agents:

Antihypertensive effect of alpha-adrenergic blockers such as guanethidine, betanidine, reserpine, alpha-methyldopa or clonidine may be potentiated by beta-blockers.

When therapy is discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blockers should be gradually discontinued several days before clonidine is discontinued, in order to reduce the potential risk of a clonidine withdrawal hypertensive crisis.

Non-steroidal anti-inflammatory drugs (NSAIDs):

Concomitant administration of non-steroidal anti-inflammatory drugs including COX-2 inhibitors with a beta-blocker, may decrease its antihypertensive effect, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by NSAIDs.

Phenothiazines:

Concurrent use with beta-blockers may result in an increased plasma concentration of either drug.

Sympathomimetic drugs:

Concomitant administration of sympathomimetic drugs such as adrenaline, noradrenaline, isoprenaline, ephedrine, phenylephrine, phenylpropanolamine, or xanthine derivatives with a non-selective beta-blocker may enhance the pressor response resulting in hypertension due to antagonistic effects.

Anaesthetic agents:

Beta-blockers and certain anaesthetics may be additive in their cardio-depressant effect. However, continued use of beta-blockers during anaesthesia reduces the risk of cardiac arrhythmias and hypertension (see PRECAUTIONS). Anaesthetic agents causing myocardial depression, such as cyclopropane and trichloroethylene, are best avoided.

Anti-arrhythmic agents:

Concomitant administration of beta-blockers with class I anti-arrhythmic agents such as disopyramide, tocainide, flecainide or amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect. Although this potentiation effect is weak for pindolol, the possibility of interactions with anti-arrhythmic agents can not be eliminated.

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.

Ergot alkaloid:

Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Cimetidine:

Cimetidine is a moderate inhibitor of multiple cytochrome enzymes such as CYP2D6, CYP3A4, CYP2C19, CYP2E1, CYP2C9, and CYP1A2. Concomitant administration of cimetidine may inhibit the hepatic metabolism of pindolol resulting in increased plasma concentrations of pindolol.

ADVERSE EFFECTS

Adverse drug reactions have been derived from post-marketing experience with Visken. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

The adverse drug reactions are, in most cases, mild and transient in nature, and the necessity for interruption of Visken therapy is rarely observed (also see PRECAUTIONS).

Adverse drug reactions are listed according to system organ classes in MedDRA.

Psychiatric disorders:	sleep disorders (similar to those observed with other beta-blockers), depression, hallucinations
Nervous system disorders:	dizziness, tremor, headache, paraesthesia
Cardiac disorders:	bradycardia, conduction disorder, cardiac failure
Vascular disorders:	hypotension, symptoms of peripheral vascular disorders (peripheral coldness), Raynaud's-like symptoms
Respiratory, thoracic and mediastinal disorders:	bronchospasm, dyspnea
Gastrointestinal disorders:	nausea, vomiting, diarrhoea, abdominal discomfort
Skin & subcutaneous tissue disorders:	skin reaction, hyperhidrosis, worsening of psoriasis, pruritus, erythematous rashes, allergic psoriasiform rashes (but not severe oculomucocutaneous syndrome; see PRECAUTIONS)
Musculoskeletal disorders:	muscle cramps, aching legs, cold extremities
Ocular:	keratitis and conjunctivitis
General disorders & administration site conditions:	weakness, fatigue

DOSAGE AND ADMINISTRATION

Dosage

The dosage should be adapted to the requirements of the individual patient.

Hypertension:

The usual dosage is 15 mg per day; most patients respond to 10 to 30 mg daily. Up to 15 mg may be given as a single daily dose usually in the morning. Doses above 15 mg should be divided into 2 or 3 daily doses.

In mild and moderate hypertension Visken alone may be sufficient. In more severe or in resistant cases addition of other antihypertensive drugs may be required.

Angina pectoris:

7.5 to 20 mg daily, generally divided into 3 single doses.

Cardiac arrhythmias:

15 to 30 mg daily, generally divided into 3 single doses.

Functional hyperadrenergic cardiac disturbances:

10 to 20 mg daily.

Administration

Visken tablets may be taken with or without food.

OVERDOSAGE

Symptoms

An overdose of a beta blocker may lead to pronounced bradycardia, nausea, vomiting, orthostatic disturbances, collapse, hypotension, cardiac failure, cardiogenic shock, conduction abnormalities, cardiac arrest, dyspnea, bronchospasm, hypoglycaemia, depressed levels of consciousness, generalized convulsions, coma and death. In rare circumstances, overdose of beta-blockers with intrinsic sympathomimetic activity (ISA), like Visken, may present with tachycardia and hypertension. Concomitant ingestion of alcohol, antihypertensives, antidepressants, or antiarrhythmic may aggravate the signs and symptoms of overdose.

Treatment

Contact the Poisons Information Centre on 131 126 for advice on management.

In case of overdosage or hypersensitivity to beta-blockers (very rare), 0.5 to 1 mg (or more) atropine sulphate should be given intravenously.

Should bronchospasm occur in susceptible patients, therapy with a beta₂ stimulant such as salbutamol or terbutaline or therapy with aminophylline may be considered. If necessary, isoprenaline hydrochloride may be given by slow intravenous injection beginning with approximately 5 microgram/min until the desired effect is achieved, in order to stimulate beta-adrenergic receptors. In refractory cases one may consider the intravenous administration of 8 mg to 10 mg of glucagon hydrochloride. The injection may be repeated within one hour and followed, if necessary, by an intravenous infusion of 1 mg to 3 mg per hour. The patient must be continuously monitored during these procedures.

PRESENTATION AND STORAGE CONDITIONS**Presentation**

5 mg tablets: white, marked SANDOZ one side, scored and marked LB on reverse. 100's (not supplied).

15 mg tablets: circular, flat, bevelled edge, white tablet, deep scored and marked JU on one side. 50's blister pack.

Storage

Store below 30°C.

POISON SCHEDULE

(S4) Prescription Only Medicine

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

North Ryde NSW 2113

® = Registered Trademark

ARTG START DATE

21 August 1991

DATE OF MOST RECENT AMENDMENT

14 November 2011

For internal use only

(vis291111i.doc) based on 12 May 2011 CDS