14.11.1991

VISKEN®
β-adrenoceptor blocking agent

Composition
Pindolol*

Tablets		1, 2.5, 5, 10 or 15 mg
Retard tablet		20 mg
Oral solution	1 mL (~ 20 drops) =	5 mg
Ampoules of 2 mL		0.4 mg

*INN rec.

Properties

VISKEN is a potent β-adrenoceptor antagonist (β-blocker). It blocks both β_1- and β_2-adrenoceptors for more than 24 hours after administration. It has negligible membrane-stabilising activity. As a β-blocker, VISKEN protects the heart from β-adrenoceptor stimulation during physical exercise and mental stress and also reduces the sympathetic drive to the heart at rest. Its intrinsic sympathomimetic activity (ISA), however, provides the heart with basal stimulation similar to that elicited by normal resting sympathetic activity, with the result that heart rate and contractility at rest and intracardiac conduction are not unduly depressed. The risk of bradycardia is therefore small and a normal cardiac output is not reduced.

VISKEN is a β-blocker with a clinically relevant vasodilator activity. This results from the partial agonism exerted on β_2-adrenoceptors in blood vessels. The high vascular resistance of established hypertension is lowered by VISKEN; tissue and organ perfusion is not impaired and may even be improved.

In contrast to the potentially adverse changes in blood lipoprotein profiles seen during treatment with other β-blockers (a decrease in the HDL/LDL ratio), the ratio of high density lipoproteins (HDL) to low density lipoproteins (LDL) does not change during long-term therapy with VISKEN, because of its pronounced ISA. This ISA, exerted on bronchial smooth muscle, reduces the risk of bronchospasm in non-asthmatic subjects with obstructive lung disease.

The low therapeutic doses of VISKEN reflect its high potency and bioavailability. The latter, resulting from near-complete absorption and a negligible hepatic first-pass effect, reduces individual plasma level variations and thus leads to constant therapeutic effects at a given dosage.

Slow release of the active substance from VISKEN retard tablets avoids high initial peaks and maintains therapeutic plasma concentrations over 24 hours.

Pharmacokinetics

The rapid, almost complete absorption (≥ 95%) and the negligible hepatic first-pass effect (13%) of VISKEN result in a high bioavailability (87%). Maximum plasma concentration is reached within 1 hour of oral administration. VISKEN has a plasma protein binding of 40%, a volume of distribution of 2 to 3 L/kg, and a total clearance of 500 mL/min. The elimination half-life of VISKEN is 3 to 4 hours; 30 to 40% is excreted unchanged in the urine, while 60 to 70% is excreted via kidney and liver as inactive metabolites. VISKEN crosses the placental barrier and passes in small quantities into breast milk.

Indications

- Arterial hypertension
- Angina pectoris (prevention of attacks)
- Sinus and atrial tachycardia, paroxysmal tachycardia, tachycardia in patients with atrial flutter or fibrillation, supraventricular extrasystoles
- Hyperkinetic heart syndrome

Dosage and administration

Oral: The dosage should be adapted to the requirements of the individual patient and is usually within a range of 5 to 30 mg per day.

Arterial hypertension
Doses of 5 to 15 mg may be given as a single daily dose in the morning. Doses of 20 mg should be either divided into 2 daily doses or given once a day in retard tablet form. In mild and moderate hypertension, VISKEN alone is often sufficient. In more severe or resistant cases, additional therapy with other antihypertensive drugs may be necessary.

Angina pectoris and cardiac arrhythmias
The daily dosage of 10 to 30 mg is generally divided into 2 or 3 single doses; once-a-day dosage can be used with the retard tablet.

Hyperkinetic heart syndrome
7.5 to 20 mg per day

Parenteral: This is only for emergency use in hospitals, especially in cases of cardiac arrhythmias. VISKEN should be given by slow i.v. injection with continuous monitoring of heart rate and blood pressure.

Initial dose: 2 mL (0.4 mg) i.v.
Further doses of 1 mL (0.2 mg) may be given at intervals of 20 minutes up to a total dose of 6 mL (1.2 mg).

Children: Experience with VISKEN in children is limited.

Patients with impaired kidney or liver function may usually be treated with normal doses. Only in severe cases may a reduction of the daily dose be necessary.

Contraindications
Bronchial asthma; digitalis-resistant cardiac failure, cor pulmonale, marked bradycardia, 2nd and 3rd degree A-V block

Precautions

Although VISKEN produces less depression of resting myocardial function than β-blockers without ISA, patients with incipient or manifest heart failure must be adequately digitalised before treatment with VISKEN. Similarly, if VISKEN is used for the treatment of acute myocardial infarction, it is necessary to monitor cardiovascular parameters closely.

Because of its intrinsic sympathomimetic activity, VISKEN generally causes no significant changes in pulmonary function in patients with a tendency to bronchospasm due to non-asthmatic chronic obstructive lung disease. However, as with any β-blocker, a bronchoconstrictor effect can never be completely excluded, and β-blockers should never be administered to patients with a history of bronchial asthma. Should bronchospasm occur, appropriate therapeutic measures should be taken (β_2-stimulant, theophylline derivative).

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

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

If patients with phaeochromocytoma are treated with a β-blocker, an α-blocker should always be co-administered.

β-blocker treatment is often associated with an aggravation of the symptoms of pre-existing 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 VISKEN therapy.

In severe renal failure, further impairment of renal function has been only rarely observed during therapy with VISKEN.

Care must be exercised when β-blockers are administered to patients receiving antidiabetic therapy, since hypoglycaemia may occur during prolonged fasting and some of its symptoms (tachycardia, tremor) are masked. However, patients can be trained to recognise sweating as the principal symptom of hypoglycaemia during β-blocker therapy.

Experimental studies in animals provide no evidence of a teratogenic effect of VISKEN. In the treatment of pregnant women presenting with hypertension, the drug has been shown to be effective and well tolerated without causing unfavourable effects in the foetus except, on rare occasions, bradycardia or hypoglycaemia in the newborn as a possible consequence of β-adrenoceptor blockade.
VISKEN passes in small quantities into breast milk, but it is unlikely to affect the infant when therapeutic doses are used.

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

VISKEN should be kept out of the reach of children.

Interactions

Antidiabetics: see under *Precautions*

Calcium-channel blocking agents: Experience has shown that the concomitant use of oral β-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 β-blocker is combined with a verapamil-type calcium antagonist.

Cimetidine may increase the plasma level of β-blockers, possibly by interference with hepatic metabolism.

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

MAO inhibitors: Concurrent use with β-blockers is not recommended. Possibly significant hypertension may theoretically occur up to 14 days following discontinuation of the MAO inhibitor.

Non-steroidal anti-inflammatory drugs (NSAIDs): The effect of many antihypertensive agents, including β-blockers, may be reduced when they are used concurrently with these drugs, possibly as a result of the inhibition of renal prostaglandin synthesis and sodium and fluid retention caused by NSAIDs.

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

Reserpine: Concurrent use may result in an additive and possibly excessive β-adrenergic blockade.

Sympathomimetics with β-adrenergic stimulant activity and ***xanthines:*** Concurrent use with β-blockers may result in mutual inhibition of therapeutic effects; in addition, β-blockers may decrease theophylline clearance.

Side effects

VISKEN is generally well tolerated. The side effects include: tiredness, dizziness, muscle cramps, tremor; gastrointestinal disturbances (mainly nausea); headache, sleep disturbances (similar to those observed with other β-blockers). These side effects are, in most cases, mild and transient. Skin reactions and psychic symptoms (depression, hallucinations) necessitating interruption of therapy are rarely observed (see also *Precautions*).

Treatment of overdosage

Overdosage with VISKEN usually requires no special treatment. If, in severe cases, therapy is required, 0.5 to 1.0 mg (or more) atropine sulphate should be given i.v. Alternatively, in order to stimulate the β-adrenergic receptors, isoprenaline hydrochloride may be given by slow i.v. infusion, beginning with approx. 5 µg/min until the desired effect is achieved. In refractory cases, the i.v. administration of 8 to 10 mg glucagon hydrochloride may be effective; the injection may be repeated and followed, if necessary, by an i.v. infusion of 1 to 3 mg/hour. The patient must be continuously monitored during these procedures.