VISKALDIX® / VISKALDIX® MITE
For the treatment of hypertension

Composition

	VISKALDIX	VISKALDIX MITE
Each scored tablet contains		
Pindolol*	10.0 mg	5.0 mg
Clopamide	5.0 mg	2.5 mg

* INN rec.

Properties

VISKALDIX and VISKALDIX MITE are a combination of the β-adrenoceptor blocking drug pindolol and the thiazide-type diuretic clopamide; both components lower blood pressure, but by different mechanisms of action. Clinical studies have shown that the combination is effective and well tolerated, that both components contribute to this effect, and that it is more effective than either of the two components alone.

Pindolol 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-stabilizing activity. As a β-blocker, pindolol protects the heart from β-adrenoceptor stimulation by catecholamines 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 neither resting heart rate and contractility nor intracardiac conduction are unduly depressed. The risk of bradycardia is therefore small and a non-elevated cardiac output is not reduced.

Pindolol is a β-blocker with clinically relevant vasodilator activity. This results from the ISA exerted on β_2-adrenoceptors in blood vessels. The high vascular resistance in established hypertension is lowered by pindolol; tissue and organ perfusion are 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 and thiazide-type diuretics (a decrease in the HDL/LDL ratio), the ratio of high density lipoproteins (HDL) to low density lipoproteins (LDL) remains unchanged during long-term VISKALDIX or VISKALDIX MITE therapy, owing to the pronounced ISA of pindolol. The ISA of pindolol exerted on bronchial smooth muscle also reduces the risk of bronchospasm in non-asthmatic subjects with obstructive lung disease.

Clopamide is a salidiuretic of the thiazide type belonging to the group of sulphonamide derivatives. It enhances the elimination of sodium and chloride by inhibiting their re-absorption in the renal tubules and this, in turn, leads to increased water excretion. The diuretic effect is proportional to the dosage. It is manifest 1 to 2 hours after administration and is maximal after 3 to 6 hours. The average duration of action is 12 to 18 hours, depending on dosage.

As with other diuretics, the mechanism of action of clopamide in lowering blood pressure is not known, but may be related to a reduction in blood volume or an effect on arteriolar smooth muscle which reduces peripheral resistance.

In the dosage present in VISKALDIX and VISKALDIX MITE, clopamide helps to lower blood pressure without causing excessive diuresis. It has been shown that administering it in combination with pindolol avoids excessive excretion of potassium and magnesium.

The low therapeutic doses of both drugs reflect their 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.

A clear antihypertensive effect of the combination is often seen after a few days, but 2 to 3 weeks' treatment may be necessary to achieve the full effect.

Pharmacokinetics

The pharmacokinetics of the two active ingredients are very similar and are not influenced by their combination or by being taken with food.

Both components are rapidly and almost completely absorbed. They show negligible hepatic first-pass metabolism, and the bioavailability of both is at least 85%. The maximum plasma concentration of pindolol is reached within 1 hour of ingestion, and that of clopamide 1 to 2 hours after ingestion. Plasma protein binding is 40% for pindolol and 46% for clopamide. The volume of distribution is about 2 L/kg for pindolol and 1.5 L/kg for clopamide. The total body clearance of pindolol is 400 mL/minute, that of clopamide is 165 mL/min. The elimination half-life is 3 to 4 hours for pindolol and 6 hours for clopamide. Approximately one third of the dose of both drugs is excreted unchanged in the urine. The excretion of clopamide occurs mainly via the kidneys, whereas pindolol shows a balanced excretion between the renal and hepatic routes.

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

Indications

Hypertension of all grades of severity and of all types

Dosage

VISKALDIX

Initially ½ or 1 tablet of VISKALDIX daily with breakfast. If blood pressure is not satisfactorily lowered after 2 to 3 weeks, a second tablet may be given, preferably with the mid-day meal. In resistant cases, the addition of an antihypertensive vasodilator agent may be advisable.

In patients in whom ½ tablet per day proves sufficient, VISKALDIX may be replaced by 1 tablet VISKALDIX MITE for greater convenience.

VISKALDIX MITE
Initially 1 tablet of VISKALDIX MITE daily with breakfast. If blood pressure is not satisfactorily lowered after 2 to 3 weeks, a second tablet may be given or treatment with 1 tablet of VISKALDIX may be necessary.

Children
Experience with VISKALDIX or VISKALDIX MITE in children is not available.

Elderly people
No evidence exists that the dosage or tolerability of VISKALDIX or VISKALDIX MITE is affected by advanced age. However, because of the diuretic component, elderly patients should be carefully supervised, since factors sometimes associated with aging, such as poor diet or impaired renal function, may indirectly affect the dosage or tolerability.

Contraindications

Related to pindolol
Bronchial asthma, digitalis-resistant cardiac failure, cor pulmonale, marked bradycardia, 2nd and 3rd degree A-V block.

Related to clopamide
Acute glomerulonephritis; severe renal or hepatic failure; severe or resistant hypokalaemia; hypersensitivity to sulphonamides or their derivatives (clopamide belongs to this class); hypercalcaemia; Addison's disease, pregnancy (thiazide-type diuretics should be avoided during pregnancy)

Precautions

Patients with incipient or manifest heart failure should be adequately digitalized before treatment with VISKALDIX or VISKALDIX MITE.

Because of its intrinsic sympathomimetic activity, pindolol 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).

During general anaesthesia in patients needing a β-blocker, careful monitoring of cardiovascular function is essential. When β-blockade is discontinued before general anaesthesia, the dosage of VISKALDIX or VISKALDIX MITE should be progressively reduced.

Pindolol is less likely to give rise to a rebound hypersensitivity to β-adrenoceptor stimulation following abrupt cessation of chronic therapy than are β-blockers without ISA. However, if interruption of therapy is considered necessary, it is advisable to reduce the dose of VISKALDIX or VISKALDIX MITE progressively.

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

Treatment with a β-blocker is often associated with an aggravation of the symptoms of pre-existing peripheral vascular disease. However, because of the sympathomimetic effects of pindolol mediated at the vascular β_2-receptors (vasodilatation), peripheral vascular side effects (cold extremities) are only rarely encountered during therapy with VISKALDIX or VISKALDIX MITE.

Potassium levels should be monitored in patients with kidney or liver failure, as should uric acid levels in patients suffering from gout.

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.

Dilutional hyponatraemia may occur in hot weather in oedematous patients on VISKALDIX or on VISKALDIX MITE. The appropriate therapy is water restriction, rather than the administration of salt, except in rare instances when the hyponatraemia is life-threatening. In true salt depletion, appropriate replacement is the treatment of choice.

VISKALDIX or VISKALDIX MITE should not be given to breast-feeding mothers in view of the possibility of sulphonamide hypersensitivity (to clopamide) in the infant.

Because dizziness or fatigue may occur during the initial phase of treatment with antihypertensive drugs, patients driving a vehicle or operating machinery should exercise caution until they have determined their individual reaction to treatment.

VISKALDIX and VISKALDIX MITE should be kept out of the reach of children.

Interactions

Experience has shown that the concomitant use of oral β-blockers and calcium antagonists can be useful in hypertension, but the i.v. injection of calcium channel blockers must be avoided. Concomitant oral treatment with calcium channel blockers requires careful monitoring, especially when a β-blocker (pindolol in VISKALDIX and VISKALDIX MITE) is combined with a verapamil-type calcium antagonist.

Since thiazide-type diuretics lower the renal lithium clearance, the dosage of lithium should be reduced and plasma levels of lithium should be carefully monitored during concomitant treatment with VISKALDIX or VISKALDIX MITE and lithium preparations.

Corticosteroids and non-steroidal anti-inflammatory drugs may diminish the excretion of sodium and water, so that co-administration with VISKALDIX or VISKALDIX MITE may

necessitate an additional dose of a diuretic. The effect of oral anticoagulants may be reduced by thiazide diuretics.

Side effects

VISKALDIX and VISKALDIX MITE are generally well tolerated. The following are occasionally observed: dizziness, tiredness, gastrointestinal disturbances, sleep disturbances (similar to those observed with other β-blockers and their combinations). These side effects are, in most cases, mild and transient.

Skin reactions and psychic symptoms (depression, hallucinations), necessitating interruption of therapy, are rarely observed. Thrombocytopenia and leucopenia have been reported in isolated cases during treatment with thiazide diuretics.

Overdosage

Symptoms: bradycardia, nausea, vomiting, orthostatic disturbances, syncope, hypokalaemia and its accompanying disorders.

Treatment: in the case of overdosage or hypersensitivity to β-blockers (very rare), 0.5 to 1.0 mg (or more) atropine sulphate should be given i.v. If necessary, in order to stimulate the β-adrenoceptors, isoprenaline hydrochloride may be given by slow i.v. injection beginning with approx. 5 µg/min until the desired effect is achieved. In refractory cases, the i.v. administration of 8 to 10 mg of 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. If indicated, the electrolyte balance should be restored.