Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

VISKALDIX 10mg/5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of pindolol and 5mg of clopamide.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, round, uncoated, flat, bevelled-edge tablets of 7 mm in diameter, having a single break-line and code 7 D on one side and branded ‘SANDOZ’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Mild to moderate hypertension.

4.2 Posology and method of administration

Adults

The recommended dose is one tablet daily to be taken in the morning. If the blood pressure is not satisfactorily controlled after 2 or 3 weeks, a second tablet may be given with the mid day meal. A maximum dose of 3 tablets daily may be taken if necessary.

Children

Not recommended.

Use in the Elderly

No evidence exists to suggest that the dosage or tolerability of VISKALDIX is directly affected by advanced age. However, because of the diuretic component, such patients should be carefully supervised as factors commonly associated with ageing, such as poor diet or impaired renal function may indirectly affect the dosage or tolerability.

Method of Administration

Oral.

4.3 Contraindications

Untreated cardiac failure (see also precautions), sick sinus syndrome (including sino – atrial block), second and third degree heart block, Prinzmetal's angina, untreated phaeochromocytoma, metabolic acidosis, pronounced bradycardia, cor pulmonale, refractory hypokalaemia, hyponatraemia, hypercalcaemia, Addison's disease, severe renal or hepatic impairment and symptomatic hyperuricaemia.

VISKALDIX should not be used with agents which inhibit calcium transport e.g. verapamil.

4.4 Special warnings and precautions for use

Especially in patients with ischaemic heart disease treatment should not be discontinued suddenly. The dosage should be gradually reduced i.e. over 1- 2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris.

Patients with poor cardiac reserve should be stabilised before treatment with VISKALDIX to prevent impairment of myocardial contractility.

As with all beta-blockers, VISKALDIX should be used with caution in patients with a history of obstructive lung disease, recent myocardial infarction or thyrotoxicosis. VISKALDIX can be administered with caution to patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the beta-blocker, depending on the degree of airway resistance and the benefit derived from beta-blockade.

Patients with spontaneous hypoglycaemia or diabetes should be monitored closely as concomitant use of beta-blockers may intensify the blood sugar lowering effect of insulin and other anti-diabetic drugs. Also thiazide diuretics can lower insulin tolerance. Use of beta-blockers may mask the symptoms of hypoglycaemia (tachycardia, tremor).

During treatment with VISKALDIX patients should not undergo anaesthesia with agents causing myocardial depression (e.g. halothane, cyclopropane, trichloroethylene, ether, chloroform). VISKALDIX should be gradually withdrawn before elective surgery. In emergency surgery or cases where withdrawal of VISKALDIX would cause deterioration in cardiac condition, 1 to 2mg of atropine sulphate administered intravenously, might be necessary to prevent severe bradycardia, but expert advice should be sought.

If a beta-blocker is indicated in a patient with phaeochromocytoma it must always be given in conjunction with an alpha-blocker. Pre-existing peripheral vascular disorders may be aggravated by beta-blockers.

Patients with known psoriasis should take beta-blockers only after careful consideration.

Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

In renal failure a further impairment of renal function following beta blockade has been reported in a few cases. In such patients it may be necessary to increase the intervals between the doses or to reduce the dosage of the drug.

Potassium levels should be checked in patients with renal or hepatic failure and urate levels should be checked in patients with gout. On rare occasions hyperuricaemia may occur whilst takingVISKALDIX; no case of acute gout has so far been reported.

The preparation should be used with caution in elderly patients, in those with impaired hepatic or renal function, in those with potential obstruction of the urinary tract, or with disorders rendering their electrolyte balance precarious.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

VISKALDIX should not be used during concomitant administration of lithium or by patients with known hypersensitivity to sulphonamides.

Calcium-channel blocking agents: VISKALDIX should not be used with calcium–channel blockers with negative ionotropic effects e.g. verapamil and to a lesser extent diltiazem. 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 IV route must be avoided. The concomitant use with dihydropyridines e.g. nifedapine may increase the risk of hypotension. In patients with cardiac insufficiency, treatment with beta-blocking agents may lead to cardiac failure.

Use of digitalis glycosides in association with beta-blockers may increase atrio-ventricular conduction time.

Clonidine: 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.

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.

Caution should be exercised in the concurrent use of beta-blocking agents with class 1 anti-arrhythmics (e.g. disopyramide, quinidine, lignocaine, procainamide) and amiodarone.

Concomitant use of beta-blockers may intensify the blood sugar lowering effect of insulin and other anti-diabetic drugs.

Cimetidine, hydralazine and alcohol may induce increased plasma levels of hepatically metabolised b-blockers.

Sympathomimetics with beta–adrenergic stimulant activity, a-adrenoceptor stimulants (e.g. noradrenaline) and xanthines: concurrent use with beta-blockers may result in mutual inhibition of therapeutic effects. In addition, beta blockers may decrease theophylline clearance.

Concomitant use of beta-blockers with tricyclic anti-depressants, barbiturates and phenothiazines as well as other anti-hypertensive agents such as neurone blocking agents (e.g. guanethidine or bethanidine and reserpine) and diuretics may increase the blood pressure lowering effect.

Reserpine: concurrent use may result in an additive and possibly excessive beta adrenergic blockade.

The concomitant administration of this preparation with cardiac glycosides or non- depolarising muscle relaxants may necessitate adjustment of the dosage of these drugs.

4.6 Pregnancy and lactation

VISKALDIX is contra–indicated in pregnancy and should not be given to lactating women in view of the possibility of sulphonamide hypersensitivity (due to clopamide) in the infant.

4.7 Effects on ability to drive and use machines

Because dizziness or fatigue may occur during the initial phase of treatment with anti- hypertensive drugs, patients driving vehicles or operating machinery should exercise caution until their individual response to treatment has been determined.

4.8 Undesirable effects

Side effects associated with beta-blockade: bradycardia, a slowed AV–conduction or increase of an existing AV-block, hypotension, heart failure, cold and cyanotic extremities, Raynaud's phenomenon, paraesthesia of the extremities, increase of an existing intermittent claudication, fatigue, headaches, impaired vision, hallucinations, psychoses, confusion, impotence, dizziness, sleep disturbance, depression, nightmares. Gastro-intestinal problems, nausea, vomiting, diarrhoea, bronchospasm in patients with bronchial asthma or a history of asthmatic complaints, disorder of the skin, especially rash, dry eyes. Beta-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia. An increase in ANA (anti nuclear antibodies) has been seen; its clinical relevance is not clear.

Thiazide diuretics may cause postural hypotension and mild gastrointestinal effects; impotence (reversible on withdrawal of treatment); hypokalaemia, hypomagnesaemia, hyponatraemia, hypercalcemia, hypochloraemic alkalosis, hyperuricaemia, gout, hyperglycaemia, and increases in plasma cholesterol. Less commonly rashes, photosensitivity; blood disorders hypersensitivity reactions (including pneumonitis, pulmonary oedema, severe skin reaction) have also been reported.

4.9 Overdose

Overdose may cause alterations in heart rate, nausea, vomiting, orthostatic disturbances, collapse, hypokalaemia and its accompanying disorders.

Treat by elimination of any unabsorbed drug and general supportive measures.

Plasma electrolytes should be closely monitored. Marked bradycardia as a result of overdosage or idiosyncrasy should be treated with atropine sulphate, 1 to 2 mg intravenously. If necessary, isoprenaline hydrochloride can be administered by a slow intravenous injection and under constant supervision beginning with 25 micrograms (5mcg/min) until the desired effect is achieved. A cardiac pacemaker may be required; IV glucagon (5 to 10mg) has been reported to overcome some of the features of serious overdosage and may be useful.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

VISKALDIX is a combination of pindolol and clopamide, both acting to lower pressure, although by two separate mechanisms.

Pindolol is a non–selective beta–adrenergic antagonist which blocks both ß1 and ß2 adrenoceptors for more than 24 hours following administration. It has negligible membrane stabilising activity. The intrinsic sympathomimetic activity (ISA) provides the heart with basal stimulation similar to that elicited by normal resting sympathetic activity. Thus resting cardiac output and heart rate are not unduly depressed, subsequently reducing the risk of bradycardia.

Clopamide enhances the elimination of sodium and chloride by inhibiting their re – absorption in renal tubules which in turn leads to increased water excretion. The mechanistic relationship of the diuretic action and reduced blood pressure is not fully understood, however the diuretic effect is proportional to the dosage. Diuresis is initiated after 2 hours and lasts for up to 24 hours with maximal effect after 3 to 6 hours.

This combination can produce a clear anti-hypertensive effect after a few days, but in some cases to achieve the full effect 2 to 3 weeks treatment may be necessary.

5.2 Pharmacokinetic properties

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. Thus the bioavailability of both is at least 85%. The maximum plasma concentration of pindolol is reached within 1 hour after 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 2l/kg for pindolol, and 1.5l/kg for clopamide. The total body clearance of pindolol is 400ml/min, that of clopamide is 165ml/min. The elimination half-life is 3 – 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.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Maize starch
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Clear PVC/PVdC/Foil blister packs containing 28 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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