SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

PHYSIOTENS 0,2 (Film-coated tablets)
PHYSIOTENS 0,3 (Film-coated tablets)
PHYSIOTENS 0,4 (Film-coated tablets)

COMPOSITION:

Each film-coated tablet contains 0,2. 0,3 or 0,4 mg moxonidine

PHARMACOLOGICAL CLASSIFICATION:

A. 7.1.3 Other hypotensives.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

In different animal models moxonidine has been shown to have antihypertensive effects. Available experimental data suggest that the site of the antihypertensive action of moxonidine is the central nervous system. Within the brainstem, moxonidine has been shown to selectively interact with I_1-imidazoline receptors. These imidazoline-sensitive receptors are concentrated in rostral ventrolateral medulla, an area critical to the central control of the peripheral sympathetic nervous system. The net effect of this interaction with the I_1-imidazoline receptors appears to result in a reduced activity of sympathetic nerves (demonstrated for cardiac, splanchnic and renal sympathetic nerves).

Moxonidine exhibits only low affinity to central α_2-adrenoceptors.

In humans, moxonidine leads to a reduction of systemic vascular resistance and consequently arterial blood pressure.

Pharmacokinetic properties

Absorption

Approximately 90% of an oral dose of moxonidine is absorbed; it is not subject to first-pass metabolism and its bioavailability is 88%. Food intake does not interfere with moxonidine.

Biotransformation:

Moxonidine is 10 to 20% metabolised, mainly to 4,5-dehydromoxonidine and to a guanidine derivative by opening of the imidazoline ring. The hypotensive effect of 4,5-dehydromoxonidine is only 1/10, and that of the guanidine derivative is less than 1/100 of that of moxonidine. The maximum plasma levels of moxonidine are reached 30 to 180 minutes after intake of a film-coated tablet.

Distribution:

Only approximately 7% of moxonidine is bound to human plasma protein (Vd_{ss} = 1.8 ± 0,4 l/kg).

Elimination:

Over a 24-hour period, 78% of the total dose was excreted in the urine as parent moxonidine and 13% of the dose was excreted as dehydrogenated moxonidine. Other minor metabolites in urine accounted for approximately 8% of the dose. Less than 1% is eliminated via the faeces. The elimination half-lives of moxonidine and its metabolite are approximately 2,5h and 5h respectively.

Pharmacokinetics in the elderly:

The pharmacokinetic properties of moxonidine in healthy elderly showed significantly increased t_{max} and AUC values. However, the differences were small and are unlikely to be clinically relevant.

Pharmacokinetics in Children:

As moxonidine is not recommended for use in children, no pharmacokinetic studies have been performed in this subpopulation.

Pharmacokinetics in renally impaired:

Elimination of moxonidine is significantly correlated with the creatinine clearance. In patients with moderate renal impairment (GFR 30-60 ml/min) steady-state plasma concentrations and terminal half-life are approximately 2 fold and 1.5 fold higher, respectively, compared to hypertensive patients with normal renal function (GFR > 90 ml/min). In patients with severe renal impairment (GFR < 30 ml/min), steady-state plasma concentrations and terminal half-life are approximately 3 fold higher. No unexpected drug accumulation after multiple dosing was observed in these patients. In end-stage renal patients (GFR < 10 ml/min) undergoing haemodialysis, plasma concentrations and terminal half-life are 6 fold and 4 fold higher, respectively. In all groups maximum moxonidine plasma concentrations are only 1.5 - 2 fold higher.

In renally impaired patients, the dosage should therefore be titrated according to the individual requirements.

Moxonidine is eliminated to a small extent by hemodialysis.

INDICATIONS:

Mild to moderate essential hypertension.

CONTRAINDICATIONS:

PHYSIOTENS should not be used in cases of:

- history of angioneurotic oedema,
- hypersensitivity to any of the ingredients,
- sick sinus syndrome or sino-atrial block,
- 2nd or 3rd degree atrioventricular block,
- bradycardia (below 50 beats/minute at rest),
- life threatening dysrhythmia,
- severe heart failure,
- severe coronary artery disease or unstable angina,
- severe liver disease,
- severe renal dysfunction (GFR < 30 ml/minute, serum creatinine concentration > 160 μmol/l).

PHYSIOTENS should not be used because of lack of therapeutic experience in cases of:

- intermittent claudication,
- Raynaud's disease,
- Parkinson's disease,
- epileptic disorders,
- glaucoma,
- depression,
- children below 18 years of age.

WARNINGS:

The use of **PHYSIOTENS** concomitantly with alcohol or tricyclic antidepressants should be avoided as safety and efficacy have not been demonstrated.

If **PHYSIOTENS** is used in combination with a beta-blocker and the treatment has to be stopped, the beta-blocker should be stopped first and then **PHYSIOTENS** after a few days have elapsed.

In patients with moderate renal dysfunction (GFR above 30 but below 60 ml/min, serum creatinine above 105 but below 160 μmol/l), the hypotensive effect of **PHYSIOTENS** should be closely monitored, especially at the start of treatment.
Treatment with **PHYSIOTENS** should not be discontinued abruptly. **PHYSIOTENS** should be withdrawn gradually over a period of two weeks.

No data are available to suggest that **PHYSIOTENS** adversely affects the ability to drive or operate machinery. However, as somnolence and dizziness have been reported, patients should be cautioned about their ability to undertake potentially hazardous tasks such as driving and operating machinery if so affected.

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

INTERACTIONS:
Concurrent administration of hydrochlorothiazide enhances the hypotensive effect of **PHYSIOTENS**.
The effect of sedatives and hypnotics may be intensified by **PHYSIOTENS**. The sedative effect of benzodiazepines can be enhanced by the concurrent administration of **PHYSIOTENS**.
Since tricyclic antidepressants may reduce the effectiveness of centrally acting antihypertensive agents, it is not recommended that tricyclic antidepressants be co-administered with **PHYSIOTENS**. No pharmacodynamic interaction has been demonstrated with moclobemide.

PREGNANCY AND LACTATION:
No clinical data on pregnancies are available. Safety in pregnancy has not been established.
PHYSIOTENS is excreted into breast milk. Mothers on **PHYSIOTENS** should not breastfeed their children.

DOSAGE AND DIRECTIONS FOR USE
Treatment should be started with 0,2 mg of **PHYSIOTENS** in the morning. The dose may be titrated after three weeks to 0,4 mg, given as one dose or as divided doses (morning and evening) until a satisfactory response has been achieved.

A single dose of 0,4 mg of **PHYSIOTENS** or 0,2 mg twice daily (morning and evening) should not be exceeded.

In patients with moderate renal dysfunction (GFR above 30 ml/min, but below 60 ml/min), the single dose should not exceed 0,2 mg.

The tablets should be taken with liquid. As the intake of food has no influence on the pharmacokinetic properties of moxonidine, the tablets may be taken before, during, or after a meal.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The most common side effects seen during clinical studies with **PHYSIOTENS**, more than an isolated case, are listed below, by system organ class and by frequency. The frequency and intensity of these symptoms may decrease in the course of treatment.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (< 1/1000).

Nervous system disorders

Common: Headache, dizziness, somnolence

Uncommon: Insomnia

Blood and lymphatic system disorders

Rare: Hypotension, orthostatic hypotension

Gastrointestinal disorders

Common: Dry mouth

Uncommon Nausea

Skin and subcutaneous tissue disorders

Uncommon: Skin rash, itching (pruritus)

Very rare Angioedema

General disorders

Common: Asthaenia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

The following symptoms may occur: headache, sedation, somnolence, hypotension, orthostatic hypotension and dizziness, asthaenia, bradycardia, dry mouth, vomiting, fatigue and upper abdominal pain. In addition, based on a few high dose studies in animals, hypertension, tachycardia and hyperglycaemia may occur.

No specific antidote is known. In case of hypotension, circulatory support such as fluids and dopamine administration may be considered. Bradycardia may be treated with atropine. Alpha-

receptor antagonists may diminish or abolish the paradoxical hypertensive effects of overdosage. Treatment is symptomatic and supportive.

IDENTIFICATION:

PHYSIOTENS 0,2: Light pink, round, biconvex, film-coated tablets imprinted with "0,2" on one side.

PHYSIOTENS 0,3: Pale red, round, biconvex, film-coated tablets imprinted with "0,3" on one side.

PHYSIOTENS 0,4: Dull red, round, biconvex, film-coated tablets imprinted with "0,4" on one side.

PRESENTATION:

Blister packs containing 28 or 56 tablets.

STORAGE INSTRUCTIONS:

Store below 25 ^{o}C. **KEEP OUT OF REACH OF CHILDREN**.

REGISTRATION NUMBER:

PHYSIOTENS 0,2: 32/7.1.3/0139

PHYSIOTENS 0,3: 32/7.1.3/0140

PHYSIOTENS 0,4: 32/7.1.3/0141

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

ABBOTT LABORATORIES SA (PTY) LTD
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