PACKAGE INSERT FOR DETRUNORM®

SCHEDULING STATUS:

S3

PROPRIETARY NAME (and dosage form):

DETRUNORM® Tablets

COMPOSITION:

Each tablet contains 15 mg propiverine hydrochloride.

Inactive ingredients: Lactose monohydrate, powdered cellulose, magnesium stearate, sucrose, talc, heavy kaolin, calcium carbonate, titanium dioxide (E 171), acacia gum, colloidal anhydrous silica, Macrogol 6000, glucose monohydrate, Cochineal red A (E124, lake), moutan wax.

Contains sugar – lactose monohydrate; glucose and sucrose.

PHARMACOLOGICAL CLASSIFICATION:

A.5.4 Medicines affecting autonomic functions Cholinolytics (Anticholinergics)

PHARMACOLOGICAL ACTION:

DETRUNORM® Tablets are spasmolytic and anticholinergic:

Inhibition of calcium influx causing musculotropic spasmolysis.

Pharmacodynamic properties

In animal models propiverine hydrochloride causes a dosage dependent decrease of the intravesical pressure and an increase in bladder capacity.

The effect is based on the sum of the pharmacological properties of propiverine and its three active metabolites which are directly musculotropic and anticholinergic.

Pharmacokinetic properties

Absorption

After oral administration of **DETRUNORM®** propiverine hydrochloride is rapidly absorbed from the gastrointestinal tract. Maximal plasma concentrations are reached after 2.3 hours as an average after a single dose of one coated tablet. The average absolute bioavailability of **DETRUNORM®** is 40.5 % (arithm. Mean value for $AUC_{o-\infty\ (p.o.)}/AUC_{0-\infty\ (i.v.)}$).

Distribution

Propiverine is already intensively metabolized pre-systemically.

After repeated application (15 mg two to three times a day) steady state is reached after four to five days at a higher concentration level than after single dose application ($C_{average}$ = 61 ng/ml).

The calculated volume of distribution (after 10 mg, 20 mg respectively) of approximately 253 l (125 – 473 l) indicates, that a large amount of available propiverine is distributed to peripheral compartments. The protein binding is around 90% for the parent substance and around 60% for the principal metabolite.

Metabolism

The substance has a high first pass effect. The main metabolite, the N-oxide of propiverine, is found in the blood at a concentration which greatly exceeds that of the parent substance. Two other metabolites can be detected qualitatively.

Excretion

The elimination of propiverine and its metabolites takes place via the urine (less than 20% of the dose administered), bile and faeces. The parent substance and the principal metabolite are excreted with a total clearance of 141 ml / min, the renal clearance is merely 1 ml / min. The elimination half life value is 20 hours.

The effect of food and other drugs on bioavailability

None known

Steady state characteristics of propiverine following multiple-dose administration (3 x 15 mg / 6 days) of DETRUNORM®

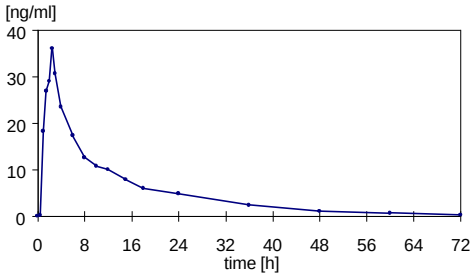
Dosage interval [h]	$AUC_{o-t(last)}$ [ngxh/ml]	[%]*	PTF [%]	[%]*	$C_{average}$ [ng/ml]	[%]*
0 - 8	515	35	57		64	64

				16		
8 – 16	460	33	70	25	57	33
16 - 24	421	36	52	39	52	36

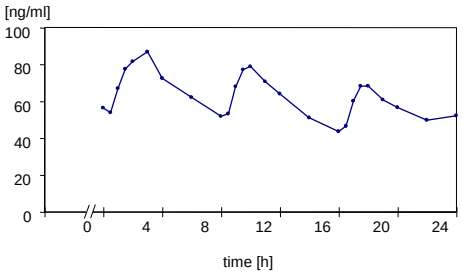
*CV: coefficient of variation

PTF: peak-trough fluctuation

Plasma level of propiverine in healthy volunteers after single and repeated (t.i.d. for 6 days) administration of coated tablets



single dose



multiple dose

Preclinical safety data

In long term oral dose studies in two mammalian species, the main treatment related effects were changes in the liver (including elevation of hepatic enzymes). These were characterized by hepatic hypertrophy and fatty degeneration. The fatty degeneration was reversible upon cessation of treatment.

In animal studies, skeletal retardation in the offspring occurred when the drug was administered orally at high doses to pregnant females. In lactating mammals propiverine hydrochloride was excreted into the milk.

There was no evidence of mutagenicity. Carcinogenicity studies in rodents revealed three types of tumours which were considered to be species specific and therefore not of clinical relevance.

INDICATIONS

The treatment of urinary incontinence, as well as urgency and frequency, in unstable bladder conditions, in patients who have either idiopathic bladder instability, or neurogenic bladder (detrusor hyperreflexia) from spinal cord injuries.

CONTRA-INDICATIONS

DETRUNORM® Tablets are contra-indicated in patients being hypersensitive to the active substance or to any of the excipients and in patients suffering from one of the following disorders:

- obstruction of the bowel
- significant degree of bladder outflow obstruction where urinary retention may be anticipated
- myasthaenia gravis
- intestinal atony
- severe ulcerative colitis
- toxic megacolon
- glaucoma
- hepatic disorders
- renal impairment
- tachyarrhythmias
- cardiac failure / dysrhythmias
- diabetes mellitus with autonomic dysfunction

Due to lack of data DETRUNORM® should not be used in children.

WARNINGS AND SPECIAL PRECAUTIONS:

During long-term therapy hepatic enzymes should be monitored, because reversible changes of liver enzymes may occur. Monitoring of intraocular pressure is recommended in patients at risk of developing glaucoma.

Particular attention should be paid to the residual urine volume in cases of urinary tract infections. DETRUNORM® should be used with caution in patients suffering from autonomic neuropathy.

Conditions that may be aggravated following administration of the drug are:

Hyperthyroidism

Coronary artery disease

Congestive heart failure (NYHA IV)

Cardiac arrhythmias

Tachycardias

Prostatic hypertrophy

Hiatus hernia with reflux oesophagitis

Cerebral sclerosis

Urinary frequency and nocturia due to renal disease or congestive heart failure as well as organic bladder diseases (e.g. urinary tract infections, malignancy) should be ruled out prior to treatment.

Effects on ability to drive and use machinery

Propiverine hydrochloride may produce drowsiness and blurred vision. The patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this medicine.

INTERACTIONS:

Interaction with other medicaments

Increased effects due to concomitant medication with tricyclic antidepressants (e.g. imipramine), tranquilisers (e.g. benzodiazepines), anticholinergics, amantadine, neuroleptics (e.g. phenothiazines) and β - sympathomimetics. Decreased effects due to concomitant medication with cholinergic medicines. Reduced blood pressure in patients treated with isoniazid. The effect of prokinetics such as metoclopramide and cisapride may be decreased.

Sedative medicines may enhance the drowsiness caused by propiverine hydrochloride.

PREGNANCY AND LACTATION:

Contra-indicated during pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE:

For oral use.

The recommended daily doses are as follows:

Adults:

As a standard dose one coated tablet (= 15 mg propiverine hydrochloride) two times a day is recommended, this may be increased to three times a day. Some patients may respond to a dosage of 15 mg a day.

For reflex incontinence a dose of one coated tablet three times daily is recommended. This may be increased to four times a day if necessary and tolerated.

Elderly:

Generally there is no special dosage regimen for the elderly.

DETRUNORM® contains 0.61 mg of glucose. When taken according to the dosage recommendations a daily dose of 2 tablets supplies 1.22 mg of glucose.

SIDE-EFFECTS

Adverse events of potential clinical relevance are listed below by system organ class.

Frequencies are defined as: very common (> 1/10); common (≥1/100, < 1/10); uncommon (≥1/1000, < 1/100); rare (≥1/ 10000, <1/1000; very rare <1/10000).

The following side-effects can be associated with the use of propiverine hydrochloride:

Gastrointestinal disorders:

Very common : dry mouth

Common: constipation

Ocular disorders:

Common: blurred vision

Urinary system disorders:

Uncommon : increased residual urine

Nervous system disorders:

Rare: restlessness, irritation

Vascular disorders:

Uncommon: decreased blood pressure, drowsiness, heat sensations

Cardiac disorders:

Very rare: tachycardia

General disorders:

Uncommon: fatigue

Skin and subcutaneous tissue:

Rare: rash due to idiosyncrasy (propiverine hydrochloride) or hypersensitivity (excipients e.g. colourant)

All side-effects are transient and recede after a dose reduction or termination of the therapy after maximum 1 – 4 days.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

A maximal dosage of 1 mg / kg body weight / day should not be exceeded. Ingestion of toxic quantities (greater than 120 mg single dose) may give rise to:
Restlessness, dizziness, muscular weakness, disorders in speech and vision, dryness of mucosa, vertigo, cardiovascular disorders.

Therapy: Initiation of vomiting or gastric lavage using an oiled tube (attention: dryness of mucosa!) followed by symptomatic treatment as in atropine overdose (e.g. physostigmine) with a dosage of 1.0 to 2.0 mg in adults by slow intravenous injection; (may be repeated as necessary to a total of 5 mg); fever should be treated symptomatically with tepid sponging or ice-packs; in cases of pronounced restlessness or excitation, diazepam may be given by intravenous injection up to 10 mg; tachycardia can be treated with propranolol; urinary retention can be treated by catheterisation; in the event of curare-like muscle paralysis, mechanical ventilation may be required.

IDENTIFICATION:

Rose-coloured, lenticular, glazing coated tablets with consistent surface.

PRESENTATION:

Strips (Alu-PVC blister foil) in carton with 10 sugar-coated tablets per strip:

30 Tablets (3 strips per carton)

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep out of reach of children

REGISTRATION NUMBER:

36/5.4/0019

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

LITHA PHARMA (PTY) LTD

106 16th Road

Midrand

1685

South Africa

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7 April 2006