PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S3

1. NAME OF THE MEDICINE

DETRUNORM® PAED 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 5 mg propiverine hydrochloride (equivalent to 4.55 mg propiverine).

Excipients with known effect: Lactose monohydrate (34 mg), glucose monohydrate (0.31 mg) and sucrose (24.5 mg)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet

White, lenticular in shape.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder or neurogenic detrusor overactivity from spinal cord injuries.

4.2. Posology and method of administration

Coated tablets for oral use

Recommended daily doses:

Paediatric population: daily average of 0.8 mg/kg body weight in two to three single doses

Posology

Body weight (kg)	**DETRUNORM® PAED** (5 mg) per day
12 – 16	1 – 0 - 1
17 – 22	1 – 1 - 1
23 – 28	2 – 0 – 2
29 – 34	2 – 1 - 2
≥ 35	2 – 2 – 2 or 3 – 0 – 3

In children with a body weight ≥ 35 kg, the maximum dose is the same as the standard dose in adults of 15 mg twice daily (2 x 3 **DETRUNORM® PAED**).

Treatment of overactive bladder should not start before 5 years of age, as organic development is still not complete in many cases. However, treatment of neurogenic detrusor overactivity due to spinal cord injuries can be started even before 5 years of age. Administration of propiverine hydrochloride to children below 1 year of age is not recommended due to a lack of data.

Treatment of children should be administered only within the framework of an overall therapeutic approach (e.g. so-called “urotherapy” in cases of idiopathic detrusor overactivity).

Due to the low active substance content, **DETRUNORM® PAED** is mainly used in children or in adults with a low body weight.

Adults: As a standard dose, 15 mg propiverine hydrochloride twice daily is recommended; an increase to three times daily is possible. Some patients may respond to a dose as low as 15 mg daily (3 x 5 mg). For neurogenic detrusor overactivity, a dose of 15 mg propiverine hydrochloride three times daily is recommended. The maximum recommended daily dose is 45 mg.

Elderly: Generally, there is no special posology for the elderly (see section 5.2).

Caution should be exercised and doctors should monitor patients carefully for side effects in the following dispositions (see sections 4.4 & 4.5):

Use in renal impairment: In patients with mild or moderate impairment of renal function, no dose adjustment is required; however, they should be treated with caution. In patients with severely impaired renal function (creatinine clearance < 30 ml/min), the maximum daily dose is 30 mg.

Use in hepatic impairment: In patients with mildly impaired hepatic function, there is no need for dose adjustment; however, treatment should proceed with caution. No studies have been performed to investigate the use of propiverine in patients with moderately or severely impaired hepatic function. Its use is therefore not recommended in these patients.

A high fat meal increases the bioavailability of propiverine. Therefore, propiverine should be taken before meals, especially in patients with renal or hepatic impairment (see section 5.2).

4.3. Contraindications

DETRUNORM® PAED is contraindicated in patients who have demonstrated hypersensitivity to the active substance or to any of the excipients listed in section 6.1 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
- myasthenia gravis
- intestinal atony
- severe ulcerative colitis
- toxic megacolon
- uncontrolled angle closure glaucoma
- moderate or severe hepatic impairment
- tachyarrhythmias

4.4. Special warnings and precautions for use

Propiverine should be used with caution in patients suffering from:

- autonomic neuropathy
- renal impairment (see section 4.2)
- hepatic impairment (see section 4.2).

Symptoms of the following diseases may be aggravated following administration of **DETRUNORM® PAED:**

- severe congestive heart failure (NYHA IV)
- prostatic enlargement

- hiatus hernia with reflux oesophagitis
- cardiac arrhythmia
- tachycardia

DETRUNORM® PAED, like other anticholinergics, induces mydriasis. Therefore, the risk to induce acute angle-closure glaucoma in individuals predisposed with narrow angles of the anterior chamber may be increased. Active substances of this class, including propiverine, have been reported to induce or precipitate acute angle-closure glaucoma.

Pollakiuria 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.

In patients receiving active substances that are potent flavin-containing monooxygenase (FMO) inhibitors such as methimazole in combination with potent CYP 3A4/5 inhibitors (e.g. ketoconazole) treatment should start with the lowest recommended dose. The dose may thereafter be titrated to a higher dose. However, caution should be exercised and physicians should monitor these patients carefully for side effects (see sections 4.5, 5.2).

This product contains glucose monohydrate, lactose monohydrate and sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Glucose monohydrate:

Patients with rare glucose-galactose malabsorption should not take this medicine.

Lactose monohydrate:

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

Sucrose:

Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

DETRUNORM® PAED is gluten free.

4.5. Interaction with other medicines and other forms of interaction

Increased effects due to concomitant treatment with tricyclic antidepressants (e. g. imipramine), tranquillisers (e.g. benzodiazepines), anticholinergics (if applied systemically), amantadine, neuroleptics (e. g. phenothiazines) and beta-adrenoceptor agonists (beta-sympathomimetics).

Decreased effects due to concomitant treatment with cholinergic medicinal products.

Reduced blood pressure in patients treated with isoniazid.

The effect of prokinetics such as metoclopramide may be decreased.

Pharmacokinetic interactions are possible with other active substances metabolised by cytochrome P450 3A4 (CYP 3A4). However, a very pronounced increase of concentrations for such active substances is not expected as the effects of propiverine are small compared to classical enzyme inhibitors (e.g. ketoconazole or grapefruit juice). Propiverine may be considered as weak inhibitor of CYP 3A4. Pharmacokinetic studies with patients concomitantly receiving potent CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole) or macrolide antibiotics (e.g. erythromycin, clarithromycin) have not been performed.

Patients receiving concomitant treatment with active substances that are potent inhibitors of CYP 3A4 combined with methimazole:

In patients receiving active substances that are potent flavin-containing monooxygenase (FMO) inhibitors such as methimazole in combination with potent CYP 3A4/5 inhibitors treatment should start with the lowest recommended dose. The dose may thereafter be titrated to a higher dose. However, caution should be exercised and physicians should monitor these patients carefully for side effects (see sections 4.4, 5.2).

4.6. Fertility, pregnancy and lactation

Pregnancy

Propiverine is not recommended during pregnancy.

There are no data from the use of propiverine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Breastfeeding

It is unknown whether propiverine or metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of propiverine or metabolites in milk (see section 5.3).

A risk to the newborn or infant cannot be excluded. Therefore, DETRUNORN® PEAD is not recommended in breastfeeding women.

Fertility

There are no human data on the effect of propiverine on fertility.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility. (see section 5.3)

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Propiverine may produce drowsiness and blurred vision. This may impair the patient's ability to exert activities that require mental alertness such as operating a motor vehicle or other machinery, or to exert hazardous work while taking this medicinal product.

Sedative active substances may enhance the drowsiness caused by propiverine.

4.8. Undesirable effects

Within each system organ class, the undesirable effects are ranked under heading of frequency using the following convention:

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data).

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

Immune system disorders

Rare:	hypersensitivity

Psychiatric disorders

Very rare:	restlessness, confusion
Not known:	hallucination

Nervous system disorders

Common:	headache
Uncommon:	tremor, dizziness, dysgeusia
Not known:	speech disorder

Eye disorders

Common:	accommodation disorder, visual impairment

Cardiac disorders

Rare:	tachycardia,
Very rare:	palpitation

Vascular disorders

Uncommon:	decreased blood pressure with drowsiness, flushing

Gastrointestinal disorders

Very common:	dry mouth,
Common:	constipation, abdominal pain, dyspepsia
Uncommon:	nausea/vomiting

Skin and subcutaneous tissue disorders

Uncommon:	pruritus
Rare:	rash

Renal and urinary disorders

Uncommon:	urinary retention, bladder and urethral symptoms

General disorders and administration site conditions

Common:	fatigue

Paediatric population

In studies with children, the following undesirable effects have been reported in addition: decreased appetite, sleep disorder and disturbance in attention.

During long-term therapy hepatic enzymes should be monitored, because reversible changes of liver enzymes might occur in rare cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms:

Overdose with the muscarinic receptor antagonist propiverine can potentially result in severe anticholinergic effects. Peripheral and central nervous system disturbances may occur, such as:

- severe dry mouth
- bradycardia, possibly leading to tachycardia in the further course
- mydriasis and accommodation disorder
- urinary retention
- inhibition of intestinal motility
- restlessness, confusion, hallucination, confabulation
- dizziness, nausea, speech disorder, muscular weakness

Treatment:

In the event of overdose with propiverine the patient should be treated with activated charcoal suspension with plenty of water.

Vomiting must not be induced.

Forced diuresis or hemodialysis is not effective to enhance the renal elimination.

In case of severe central anticholinergic effects such as hallucinations or pronounced excitation antidote treatment with physostigmine can be attempted.

Convulsion or pronounced excitation: treatment with benzodiazepines

Respiratory insufficiency: treatment with artificial respiration

Urinary retention: treatment with catheterization

Mydriasis: treatment with pilocarpine eye drops and/or darkening of the patient's room

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A.5.4 Medicines affecting autonomic functions Cholinolytics (Anticholinergics)

ATC code: G04B D06

Mechanism of action:

Inhibition of calcium influx and modulation of intracellular calcium in the urinary bladder smooth muscle cells causing musculotropic spasmolysis.

Inhibition of the efferent connection of the nervus pelvicus due to anticholinergic action.

Pharmacodynamic effects

In animal models propiverine hydrochloride causes a dose-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 three active urinary metabolites as shown in isolated detrusor strips of human and animal origin.

Paediatric population

In a randomised, placebo-controlled, double-blind phase-III study, significant efficacy (decrease in incontinence episodes and voiding frequency, increase in voided volume) was demonstrated for propiverine in children.

5.2. Pharmacokinetic properties

The following information refers to a formulation containing 15 mg propiverine hydrochloride:

General characteristics of the active substance:

Propiverine is nearly completely absorbed from the gastrointestinal tract. It undergoes extensive first-pass metabolism. Effects on urinary bladder smooth muscle cells are due to the parent compound and three active metabolites as well, which are rapidly excreted into the urine.

Absorption

After oral administration of Propiverine hydrochloride 15 mg, propiverine is rapidly absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 2.3 hours.

The mean absolute bioavailability of Propiverine hydrochloride 15 mg is 40.5% (arithmetic mean value of AUC0-∞ (p.o.) / AUC0-∞ (i.v.)).

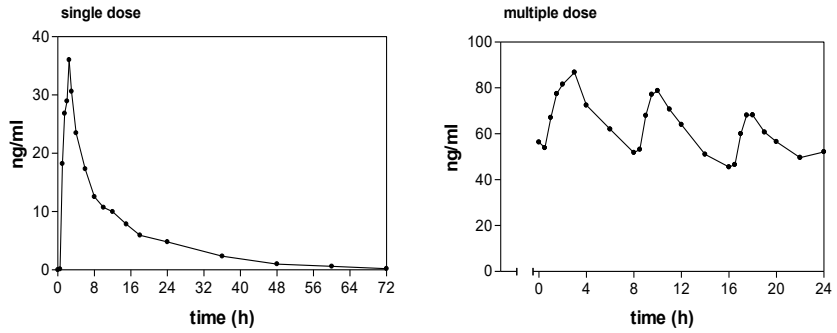
Food intake increases the bioavailability of propiverine (mean increase 1.3-fold), but does not significantly affect the maximum plasma concentrations of propiverine or its main metabolite propiverine-N-oxide. This difference in bioavailability is unlikely to be of clinical significance but adjustment of dose in relation to food intake could be required in patients suffering from impaired renal or hepatic function. Therefore, a regular intake before meals is recommended.

Distribution

After administration of Propiverine hydrochloride 15 mg t. i. d., steady state is reached after four to five days at a higher concentration level than after single dose application (Caverage = 61 ng/ml).

The volume of distribution was estimated in 21 healthy volunteers after intravenous administration of propiverine hydrochloride to range from 125 to 473 l (mean 279 l) indicating that a large amount of available propiverine is distributed to peripheral compartments. The binding to plasma proteins is 90 - 95% for the parent compound and about 60% for the main metabolite.

Plasma concentrations of propiverine in 16 healthy volunteers after single and repeated administration of Propiverine hydrochloride 15 mg (t. i. d. for 6 days):



Steady state characteristics of propiverine following multiple-dose administration to 16 healthy volunteers of Propiverine hydrochloride 15 mg (t.i.d. for 6 days):

Dose interval	AUC0-τ		PTF		$C_{average}$	
[h]	[ng·h/ml]	CV [%]	[%]	CV [%]	[ng/ml]	CV [%]
0 - 8	515	35	57	16	64	36
8 - 16	460	33	70	25	57	33
16 - 24	421	36	52	39	52	36
CV: coefficient of variation PTF: peak-trough fluctuation						

Biotransformation

Propiverine is extensively metabolised by intestinal and hepatic enzymes. The primary metabolic route involves the oxidation of the piperidyl-N and is mediated via CYP 3A4 and flavin monooxygenases (FMO) 1 and 3 and leads to the formation of the much less active N-oxide, the plasma concentration of which greatly exceeds that of the parent substance. Four metabolites were identified in urine, three of them are pharmacologically active and may contribute to the therapeutic efficacy of propiverine.
In vitro there is a slight inhibition of CYP 3A4 and CYP 2D6 detectable which occurs at concentrations exceeding therapeutic plasma concentrations 10- to 100-fold (see section 4.5).

Elimination

Following administration of 30 mg oral dose of 14C-propiverine hydrochloride to healthy volunteers, 60% of the radioactivity was recovered in urine and 21% was recovered in faeces within 12 days. Less than 1% of an oral dose is excreted unchanged in the urine. Mean total clearance after single dose administration of 30 mg is 371 ml/min (191 - 870 ml/min).

In three studies including a total of 37 healthy volunteers mean elimination half-life was 14.1, 20.1 and 22.1 hours, respectively.

Linearity/non-linearity

Pharmacokinetic parameters of propiverine and propiverine-N-oxide following oral administration of 10 – 30 mg of propiverine hydrochloride are linearly related to dose.

There are no changes of pharmacokinetics during steady state compared to single dose administration.

Characteristics in patients

Renal impairment:

Severe renal impairment does not significantly alter the disposition of propiverine and its main metabolite, propiverine-N-oxide, as deduced from a single dose study in 12 patients with creatinine clearance < 30 ml/min. No dose adjustment is to be recommended as long as the total daily dose does not exceed 30 mg propiverine hydrochloride. In case that higher dose shall be administered a careful titration of dose is recommended considering anticholinergic effects as a marker for tolerability.

Hepatic insufficiency

There were similar steady state pharmacokinetics in 12 patients with mild to moderate impairment of liver function due to fatty liver disease as compared to 12 healthy controls. No data are available for severe hepatic impairment.

Age

The comparison of trough plasma concentrations during steady state (Propiverine hydrochloride 15 mg t. i. d. for 28 days) reveals no difference between older patients (60 – 85 years; mean 68) and young healthy subjects. The ratio of parent active substances to metabolite remains unchanged in older patients indicating the metabolic conversion of propiverine to its main metabolite, propiverine-N-oxide, not to be an age-related or limiting step in the overall excretion.

Paediatric population

A dose-escalation study in children demonstrated a balanced relationship between efficacy and tolerability for the mean dose of 0.8 mg/kg body weight/per day. Up to the recommended dose range, the pharmacokinetic properties (e.g. AUC0-8, Cmax, Cav) are dose-proportional. After administration of a twice-daily dose of 0.4 mg/kg body weight, serum levels in children aged 5 to 10 years reach approximately the same values as after administration of the therapeutic dose of 15 mg propiverine hydrochloride twice daily in adults.

Patients with glaucoma

Intraocular pressure in patients with open angle glaucoma and in patients with treated (controlled) angle closure glaucoma is not increased by Propiverine hydrochloride 15 mg t.i.d. treatment for 7 days, as demonstrated by two placebo-controlled studies.

Preclinical safety data

In long-term oral dose studies in two mammalian species the main treatment-related effect were changes in the liver (including elevation of hepatic enzymes). These were characterised by hepatic hypertrophy and fatty degeneration. The fatty degeneration was reversible upon cessation of treatment. No effects on male and female fertility and reproduction behaviour were observed in toxicological studies with rats.

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

There was no evidence of mutagenicity. The carcinogenicity study in mice demonstrated an increased incidence of hepatocellular adenoma and carcinoma in high dose males. In the rat carcinogenicity study hepatocellular adenoma, kidney adenoma and urinary bladder papilloma has been demonstrated in high dose male rats, while in female animals endometrial stromal polyps were increased at the high dose levels. Both the rat and mouse tumours were considered to be species-specific and therefore not of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Tablet core:

lactose monohydrate,

cellulose, powdered,

magnesium stearate

Tablet coat:

calcium carbonate,

glucose monohydrate,

acacia gum,

macrogol 6000,

sucrose,

silica, colloidal anhydrous,

talc,

titanium dioxide (E171),

kaolin, heavy.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

5 years

6.4. Special precautions for storage

Store at or below 25 °C.

6.5. Nature and contents of container

PVC/PVDC/aluminium blisters in boxes with 28 coated tablets (2 strips per carton). Each blister strip contains 14 tablets.

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATES OF REGISTRATION

ACINO PHARMA (PTY) LTD

106 16th Road

Midrand

1685

South Africa

Under license from APOGEPHA Arzneimittel GmbH

8. REGISTRATION NUMBER

49/5.4/0967

9. DATE OF FIRST AUTHORISATION

19 July 2022

10. DATE OF REVISION OF THE TEXT

19 July 2022