

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Detrunorm XL 30 mg Modified Release Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 30 mg propiverine hydrochloride (equivalent to 27.28 mg propiverine).

Excipient(s): Lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified-release capsules, hard.

Orange and white size 3 capsules containing white to off-white pellets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of urinary incontinence, as well as urgency and frequency in patients who have idiopathic detrusor overactivity (overactive bladder).

4.2 Posology and method of administration

Capsules for oral use.

The recommended daily doses are as follows:

Adults: As a standard dose one capsule (= 30 mg propiverine hydrochloride) once a day is recommended.

Elderly: Generally there is no special dosage regimen for the elderly (see 5.2).

Children: Due to a lack of data, this product should not be used in children. There is no clinically relevant effect of food on the pharmacokinetics of propiverine (see 5.2). Accordingly, there is no particular recommendation for the intake of propiverine in relation to food.

4.3 Contraindications

The drug is contraindicated in patients who have demonstrated hypersensitivity 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
- myasthenia gravis
- intestinal atony
- severe ulcerative colitis
- toxic megacolon
- uncontrolled angle closure glaucoma
- moderate or severe hepatic impairment
- tachyarrhythmias.

This drug is also contraindicated in women who are pregnant or breast-feeding an infant.

4.4 Special warnings and precautions for use

The drug should be used with caution in patients suffering from: autonomic neuropathy.

Symptoms of the following diseases may be aggravated following administration of the drug:

severe congestive heart failure (NYHA IV)
prostatic hypertrophy
hiatus hernia with reflux oesophagitis
cardiac arrhythmia
tachycardia.

Propiverine, 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.

Drugs of this class 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.

Due to a lack of data Detrunorm XL 30 mg Capsules should not be used in children.

This medicinal product contains lactose monohydrate. 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

Increased effects due to concomitant medication 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 medication with cholinergic drugs. Reduced blood pressure in patients treated with isoniazid. The effect of prokinetics such as metoclopramide may be decreased.

Pharmacokinetic interactions are possible with other drugs metabolised by cytochrome P450 3A4 (CYP 3A4). However, a very pronounced increase of concentrations for such drugs 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 cytochrome P450 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.

4.6 Pregnancy and lactation

In animal studies, skeletal retardation in the offspring occurred when the drug was administered orally at high doses to pregnant females. The drug was also secreted into the milk of lactating mammals.

Propiverine hydrochloride should therefore not be administered to pregnant or nursing women.

4.7 Effects on ability to drive and use machines

Propiverine hydrochloride 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 drug.

Sedative drugs may enhance the drowsiness caused by propiverine hydrochloride.

4.8 Undesirable effects

Adverse reactions	System organ class (Disorders according to MedDRA)
Very common (>1/10) - dry mouth	Gastrointestinal
Common (>1/100, <1/10) - accommodation abnormal, accommodation disturbances, vision abnormal	Eye
- constipation	Gastrointestinal

Uncommon (>1/1,000, <1/100)	
- fatigue	General disorders and administration site conditions
- nausea/vomiting	Gastrointestinal
- dizziness	Nervous system
- tremor	Nervous system
- urinary retention	Urinary system
- flushing	Vascular
- decreased blood pressure with drowsiness	Vascular
Rare (>1/10,000, <1/1,000)	
- rash due to idiosyncrasy (propiverine hydrochloride) or hypersensitivity (excipients, e.g. colorant)	Skin and subcutaneous tissue
Very rare (<1/10,000, including isolated reports)	
- palpitation	Cardiac
- restlessness, confusion	Psychiatric
¹Not known (cannot be estimated from the available data)	
- hallucination	Psychiatric

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

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

4.9 Overdose

Overdose with the muscarinic receptor antagonist propiverine hydrochloride can potentially result in central anticholinergic effects, e.g. restlessness, dizziness, vertigo, disorders in speech and vision and muscular weakness.

Moreover, severe dryness of mucosa, tachycardia and urinary retention may occur.

Treatment should be symptomatic and supportive. Management of overdose may include initiation of vomiting or gastric lavage using an oiled tube (attention: dryness of mucosa!), followed by symptomatic and supportive treatment as for 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).

¹ PL20072/0016-0009; 27/08/2008

A 14-years old girl who ingested 450 mg propiverine hydrochloride presented with confabulation. The adolescent fully recovered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G04B D06

Pharmacotherapeutic group: spasmolytic, anticholinergic.

Mechanism of action

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

Inhibition of the efferent connection of the nervus pelvici 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.

5.2 Pharmacokinetic properties

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 Detrunorm XL 30 mg Capsules propiverine is absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 9.9 hours. The mean absolute bioavailability of Detrunorm XL 30 mg Capsules is $60.8 \pm 17.3\%$ (arithmetic mean value \pm SD for $AUC_{0-\infty}$ (p.o.) / $AUC_{0-\infty}$ (i.v.)).

In comparison with administration under fasting conditions, when a propiverine hydrochloride 45 mg modified release capsule is administered after a meal absorption is delayed by 1 hour, but the bioavailability of propiverine is 99%, C_{max} is 3% lower and t_{max} is identical. Food intake therefore has no significant effect on the pharmacokinetics of propiverine hydrochloride modified release capsules.

Distribution

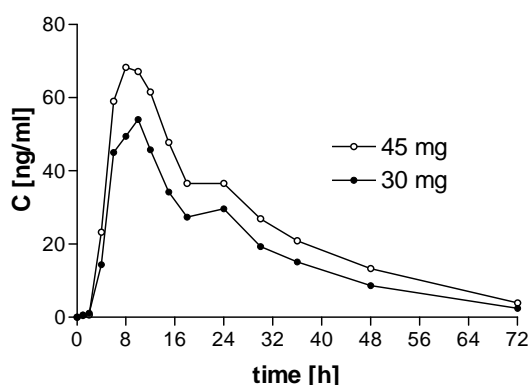
After administration of Detrunorm XL 30 mg Capsules, steady state is reached after four to five days at a higher concentration level than after single dose application ($C_{\text{average}} = 71 \text{ ng/ml}$).

The volume of distribution was estimated in 21 healthy volunteers after intravenous administration of propiverine hydrochloride to range from 125 to 473 l (mean 279l) 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.

Pharmacokinetic characteristics (geometric mean, \pm SD, range) of propiverine in 10 healthy volunteers after single dose administration of Detrunorm XL 30 mg Capsules and propiverine hydrochloride modified release capsules 45 mg:

Dose [mg]	30	45
AUC _{0-∞} [ng·h/ml]	1378 (903, 2104)	1909 (1002, 3639)
C _{max} [ng/ml]	60.6 (41.5, 88.6)	80.0 (41.8, 152.1)
t _{1/2} [h]	14.2 (10.8, 18.6)	16.3 (13.9, 19.2)
t _{max} [h]	9.9 \pm 2.4	9.9 \pm 2.4

Plasma concentrations of propiverine in 10 healthy volunteers after single dose administration of Detrunorm XL 30 mg Capsules and propiverine hydrochloride modified release capsules 45 mg:

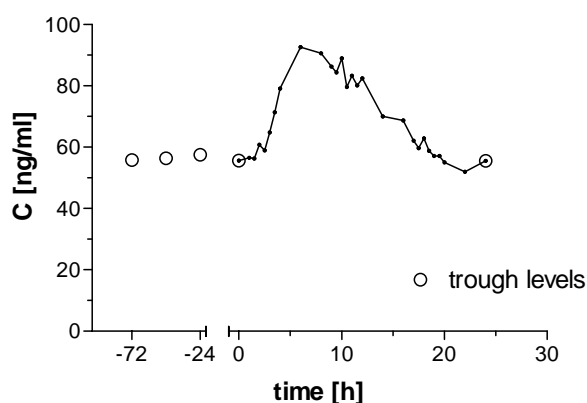


Steady state characteristics of propiverine following multiple-dose administration to 24 healthy volunteers of propiverine hydrochloride modified release capsules 45 mg once daily for 7 days:

		geometric mean	range or \pm SD
AUC _{0-24h}	[ng·h/ml]	1711	1079, 2713
PTF	[%]	109.4	81.2, 147.5
C _{av}	[ng/ml]	71	45.0, 113.0
C _{max}	[ng/ml]	105	71, 155
C _{min}	[ng/ml]	29	20, 42
t _{1/2}	[h]	20.4	12.8, 32.3
t _{max}	[h]	7.3	\pm 2.5

PTF: peak-trough fluctuation

Plasma concentrations of propiverine on day 7 and trough levels during treatment following multiple-dose administration of propiverine hydrochloride modified release capsules 45 mg to 24 healthy volunteers once daily for 7 days:



Biotransformation

Propiverine is extensively metabolised by intestinal and hepatic enzymes. The primary metabolic route involves the oxidation of the Piperidyl-N and is mediated by CYP 3A4 and Flavin-monoxygenases (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.

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).

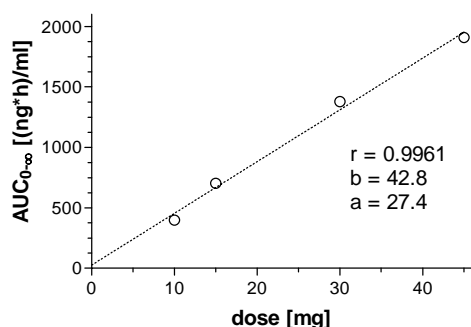
Elimination

Following administration of 30 mg oral dose of ¹⁴C-propiverine hydrochloride to healthy volunteers, 60 % of 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).

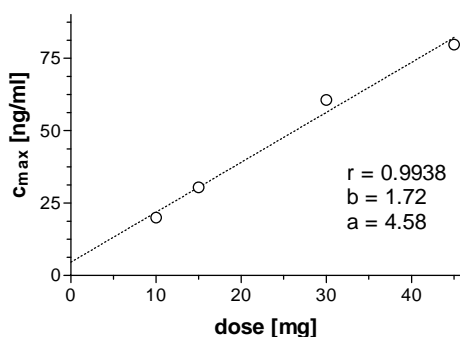
Linearity/non-linearity

Pharmacokinetic parameters of propiverine following oral administration of 10 – 45 mg of propiverine hydrochloride are linearly related to dose.

Correlation between the oral dose of extended release propiverine and the resulting $AUC_{0-\infty}$:



Correlation between the oral dose of extended release propiverine and the resulting C_{max} :



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.

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 reveals no difference between older patients (60 – 85 years; mean 68) and young healthy subjects. The ratio of parent drug 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. As bioequivalence of Detrunorm 15 mg Coated Tablets t.i.d. and propiverine hydrochloride modified release capsules 45 mg s.i.d. was established in a GCP compliant study the same can be concluded for Detrunorm XL 30 mg Capsules.

Patients with glaucoma

The treatment with Detrunorm XL 30 mg Capsules will not lead to an increase of intraocular pressure in patients with open angle glaucoma and in patients with treated (controlled) angle closure glaucoma.

5.3 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.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets

Citric acid (anhydrous)

Povidone

Lactose monohydrate

Talc

Triethyl citrate

Magnesium stearate

Methacrylic acid-methyl methacrylate copolymer (1:1)

Methacrylic acid-methyl methacrylate copolymer (1:2)

Ammonio methacrylate copolymer type A

Ammonio methacrylate copolymer type B

Capsule

Gelatin

Titanium dioxide E171

Red iron oxide E172

Yellow iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Blister

Store in the original package.

Do not store above 25°C.

6.5 Nature and contents of container

Blisters of 308µm PVC/TE/PVDC and 20µm aluminium foil in cartons with 7 or 10 or 14 capsules per blister:

Blisters:		
<u>7 per blister</u>	<u>10 per blister</u>	<u>14 per blister</u>
14 (2 blisters per carton)	20 (2 blisters per carton)	14 (1 blister per carton)
28 (4 blisters per carton)	30 (3 blisters per carton)	28 (2 blisters per carton)
49 (7 blisters per carton)		56 (4 blisters per carton)
56 (8 blisters per carton)	50 (5 blisters per carton)	84 (6 blisters per carton)
98 (14 blisters per carton)	60 (6 blisters per carton)	98 (7 blisters per carton)
112 (16 blisters per carton)	100 (10 blisters per carton)	112 (8 blisters per carton)
10 x 28 (2 blister with 14 capsules per carton)		

6.6 Special precautions for disposal

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Amdipharm Plc
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 Basildon
 Essex
 SS14 3AF
 United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 20072/0016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/04/2006

10. DATE OF REVISION OF THE TEXT

August 2008