# 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 with known effect: Lactose monohydrate (5.7 mg)
For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Modified-release capsule, hard
Orange and white size 3 capsules containing white to off-white pellets.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Symptomatic treatment of urinary incontinence and / or increased urinary frequency and urgency as may occur in patients with overactive bladder.

### 4.2 Posology and method of administration

Capsules for oral use.
Do not crush or chew the capsules.

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 dose regimen for the elderly (see section 5.2).
Paediatric population: Due to a lack of data, this product should not be used in children.

Caution should be exercised and physicians should monitor patients carefully for side effects in the following dispositions (see sections 4.4, 4.5, 5.2).
Use in renal impairment
In patients with mild or moderate impairment of renal function, no dose adjustment is required (see section 5.2).
Use in hepatic impairment
In patients with mildly impaired hepatic function, there is no need for a 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 (see section 5.2).

Patients receiving concomitant treatment with drugs that are potent inhibitors of CYP 3A4 combined with methimazole
In patients receiving drugs that are potent flavin-containing monooxygenase (FMO) inhibitors such as methimazole in combination with potent CYP 3A4/5 inhibitors treatment should start with a dose of 15 mg per day. 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).

There is no clinically relevant effect of food on the pharmacokinetics of propiverine (see section 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

**4.4 Special warnings and precautions for use**

The drug 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 the drug:
- severe congestive heart failure (NYHA IV)
- prostatic enlargement
- 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, 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.
This product contains lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

**4.5 Interaction with other medicinal products and other forms of interactions**

- 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 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 drugs that are potent inhibitors of CYP 3A4 combined with methimazole:
In patients receiving drugs that are potent flavin-containing monooxygenase (FMO) inhibitors such as methimazole in combination with potent CYP 3A4/5 inhibitors treatment should start with a dose of 15 mg per day. 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 4.2, 5.2).

**4.6 Fertility, pregnancy and lactation**

Pregnancy
There are no data from the use of propiverine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Propiverine is not recommended during pregnancy.

Breast-feeding

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. A risk to the newborn or infant cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from propiverine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 drug.
Sedative drugs 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

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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

**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 amount of water.
- Gastric lavage should only be taken into consideration with protective intubation, use of an oiled tube (dryness of mucosa) and if performed within 1 hour after ingestion of propiverine. 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**

ATC code: G04B D06
Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence

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 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.

**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 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 is 60.8 ± 17.3 % (arithmetic mean value ± SD for $AUC_{0-\infty}$ (p.o.) / $AUC_{0-\infty}$ (i.v.)).

Food does not influence the pharmacokinetics of propiverine.

The bioavailability of propiverine after the meal was 99 % compared to the fasting conditions. Administration of the ER capsule leads to mean $C_{max}$ – concentrations of propiverine of about 70 ng/ml reached within 9.5 hours after administration.

The $C_{max}$ values for the main metabolite propiverine-N-oxide were slightly increased by food (f = 1.26), whereas the extent of absorption was unchanged.

Propiverine-N-oxide showed for all pharmacokinetic parameters 90 % confidence intervals within the acceptance ranges.

An adjustment of dose in relation to food intake is not required.

Distribution

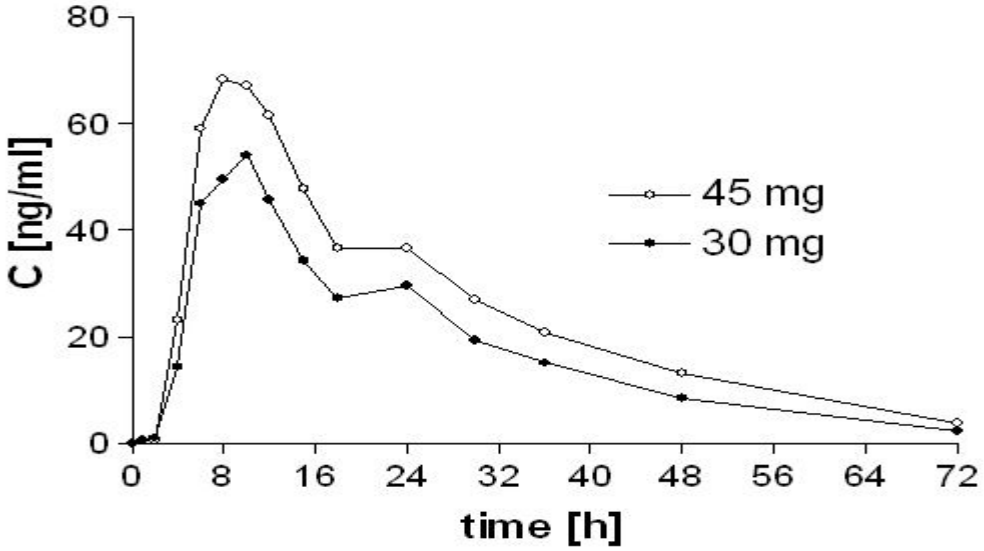
After administration of Detrunorm XL 30 mg, steady state is reached after four to five days at a higher concentration level than after single dose application ($C_{average}$ = 71 ng/ml).

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.

*Pharmacokinetic characteristics (geometric mean, ± SD, range) of propiverine in 10 healthy volunteers after single dose administration of Detrunorm XL 30 mg and Detrunorm XL 45 mg :*

| **Dose [mg]** | **30** | **45** |
|---|---|---|
| $AUC_{0-\infty}$ [ng×h/ml] | 1378<br>(903, 2104) | 1909<br>(1002, 3639) |
| $C_{max}$ [ng/ml] | 60.6<br>(41.5, 88.6) | 80.0<br>(41.8, 152.1) |
| $t_{1/2}$ [h] | 14.2<br>(10.8, 18.6) | 16.3<br>(13.9, 19.2) |
| $t_{max}$ [h] | 9.9<br>± 2.4 | 9.9<br>± 2.4 |

*Plasma concentrations of propiverine in 10 healthy volunteers after single dose administration of Detrunorm XL 30 mg and Detrunorm XL 45 mg:*

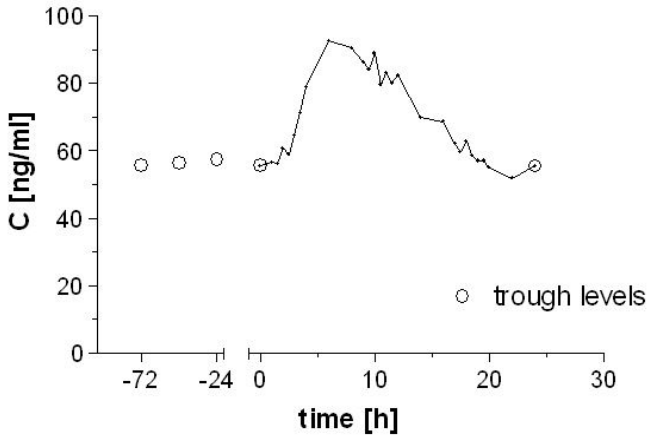



*Steady state characteristics of propiverine following multiple-dose administration to 24 healthy volunteers of Detrunorm XL 45 mg once daily for 7 days:*

| | **geometric mean** | **range or ±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 | ± 2.5 |

PTF: peak-trough fluctuation

*Plasma concentrations of propiverine on day 7 and trough levels during treatment following multiple-dose administration of Detrunorm XL 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-containing 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. 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).

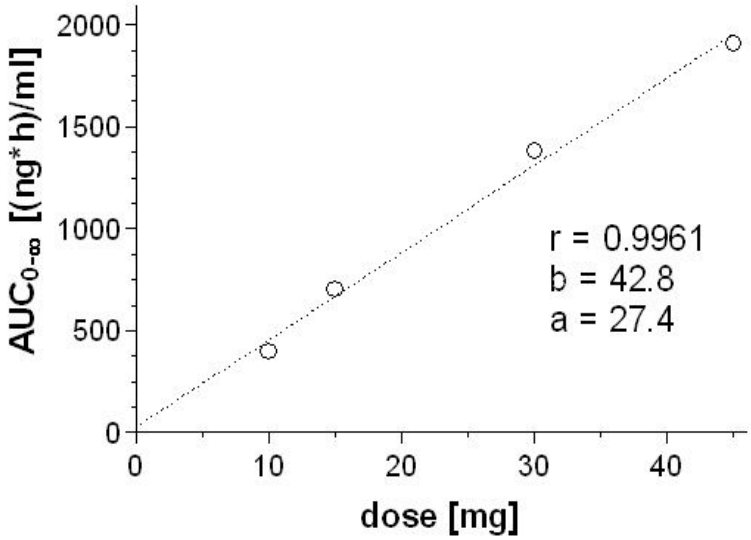
Elimination

Following administration of 30 mg oral dose of $^{14}$C-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).

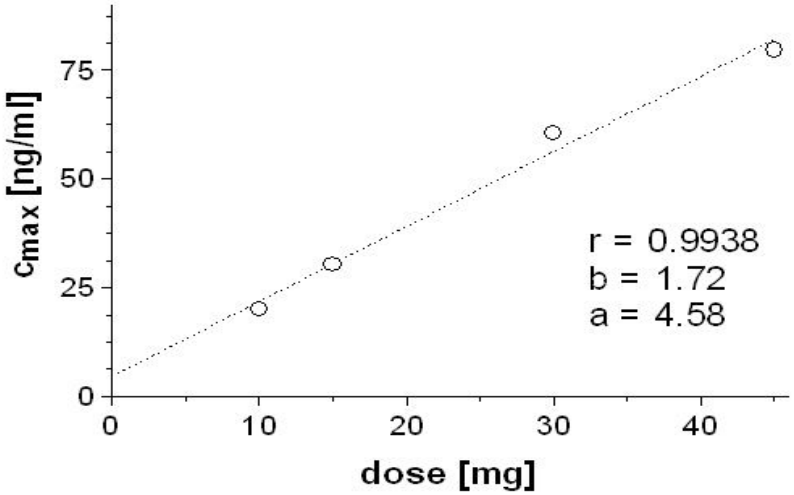
Linearity/ non-linearity

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 AUC0-∞:*




*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 coatedtTablets t.i.d. and Detrunorm XL 45 mg modified-release capsules s.i.d. was established in a GCP compliant study the same can be concluded for Detrunorm XL 30 mg.
*Patients with glaucoma:*
The treatment with Detrunorm XL 30 mg will not lead to an increase of intraocular pressure in patients with open angle glaucoma and in patients with treated (controlled) angle closure glaucoma. This was shown in two placebo-controlled studies with Detrunorm 15 mg coated tablets t.i.d. over 7 days.

**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.
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 drug 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**

**Pellets**
Citric acid
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**
Gelatine
Titanium dioxide E171
Red iron oxide E172
Yellow iron oxide E172.

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

4 years

**6.4 Special precautions for storage**

Store in the original package to protect from moisture.
Do not store above 30 ° C.

**6.5 Nature and contents of container**

Blisters of PVC/PVDC and aluminium foil in cartons of 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112 or 280 capsules.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Not applicable

**7 MARKETING AUTHORISATION HOLDER**

Consilient Health Limited
5th Floor, Beaux Lane House
Mercer Street Lower
Dublin 2
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA1876/009/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 28th September 2007
Date of last renewal: 3rd May 2011

**10 DATE OF REVISION OF THE TEXT**

June 2021