

**DETRUNORM XL 30MG MODIFIED RELEASE CAPSULES**

**PL 20072/0016**

**UKPAR**

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## **DETRUNORM XL 30MG MODIFIED RELEASE CAPSULES**

**PL 20072/0016**

### **LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Amdipharm Plc a Marketing Authorisation (licence) for the medicinal product Detrunorm XL 30mg Modified Release Capsules (PL 20072/0016). This medicine is available by prescription only.

This medicine acts as a muscle relaxant on the involuntary muscle that is found in the wall of the bladder. The relaxant reduces involuntary contractions of the bladder that can cause urinary frequency, urinary urgency and incontinence.

Detrunorm XL 30mg Modified Release Capsules raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence Marketing Authorisation has been granted.

# **DETRUNORM XL 30MG MODIFIED RELEASE CAPSULES**

**PL 20072/0016**

## **SCIENTIFIC DISCUSSION**

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## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Detrunorm XL 30mg Modified Release Capsules to Amdipharm Plc on 3 April 2006. This product can only be obtained with a prescription.

This is an national application for Detrunorm XL 30mg Modified Release Capsules submitted under Article 8.3(i) of Directive 2001/83, as a line extension to Detrunorm 15mg coated tablets (PL 20072/0015) licensed in the UK on the 15 July 2004 to Amdipharm.

Detrunorm XL 30mg Modified Release Capsules contain the active ingredient propiverine hydrochloride and is indicated for urinary incontinence and overactive bladder. Propiverine is claimed to act by inhibition of calcium influx and modulation of intracellular calcium in urinary bladder smooth muscle cells, causing musculotropic spasmodolysis. It also inhibits the efferent connection of the nervus pelvici due to anticholinergic action.

## **PHARMACEUTICAL ASSESSMENT**

### **1. INTRODUCTION**

This is an abridged application for Marketing Authorisation in the UK submitted under Article 8.3(i) of Directive 2001/83, with differences compared to the original product in pharmaceutical form and strength.

The reference product is listed as Detrunorm 15mg coated tablets (PL 20072/0015), licensed in the UK on the 15 July 2004 to Amdipharm.

The medicinal product used in the bioequivalence studies was sourced from Germany (Mictonorm) and the UK (Detrunorm). The two products have the same formula and are both manufactured by Apogepha.

A subsequent mutual recognition procedure is considered.

### **2. ACTIVE SUBSTANCE**

The active substance is manufactured by a suitable manufacturer. Propiverine hydrochloride is an antimuscarinic. The data requirements for the active substance have been included in section 3.2.S of the dossier.

Description: White crystalline powder

Chemical name: 2,2-diphenyl-2-(1-propoxy)acetic acid-(1-methylpiperid-4-yl)ester hydrochloride

Molecular formula:  $C_{23}H_{30}ClNO_3$

Relative molecular mass: 403.95

Chirality: The substance has no asymmetric centre and is not chiral.

Polymorphs: None observed

### **2. Manufacture**

#### **2.1 Manufacturer**

Propiverine hydrochloride is synthesised on a commercial scale.

An inspection certificate has been provided from the relevant authorities stating compliance to ICH-API guide Q7A, dated November 2003.

#### **2.2. Manufacturing process**

Manufacturing process

A flow diagram detailing the process has been provided. A detailed description of the process has also been included and the yields from each step have been detailed.

#### In-process controls

The in-process checks have not been detailed, with the exception of those relating to the intermediates, which are detailed in the controls of the critical steps and intermediates section below.

#### Control of starting materials

Relevant specifications and test methods have been provided for the start materials. This includes certificates of analysis.

Specifications and certificates of analysis have been supplied for the other materials used in the manufacturing process.

Confirmation that the materials used comply with the BSE/TSE requirements has been provided.

#### Control of intermediates

Reasonable details have been provided for the in-process control of the intermediates.

Acceptable certificates of analysis have been provided for each intermediate.

#### Process validation

No details are required as the process is non-biotechnological/non-biological and non-sterile in compliance with the requirements of the CTD guidance.

#### Manufacturing process development

The process is stated as being based on the published process known since 1962. Apogepha manufactured the active substance themselves from 1973 to 1991. Manufacture was then transferred to current AIM.

It is stated retrospectively that no general quality differences existed between batches at pilot scale and production scale and between batches from Apogepha and the current AIM.

### **2.3 Evidence of structure**

Structure has been demonstrated using satisfactory methods.

### **2.4 Impurities**

The key impurities resulting from the manufacturing process have been identified.

On the basis of data generated over long term production, reasonable limits have been set.

## **2.5 Control of active substance**

### Specification

Propiverine hydrochloride does not have a European Pharmacopoeia monograph. The proposed specification has been submitted by the applicant and is satisfactory.

The manufacturer of the finished drug product performs complete testing on all batches. The manufacturer responsible for packaging tests for identification and checks the certificate of analysis.

### Analytical methods

Where relevant, the test methods used are those described in the European Pharmacopoeia. In-house methods have also been used and relevant details have been provided on these methods.

### Analytical method validation

Analytical methods have been validated by submission of a comprehensive validation package complying with current guidelines.

## **2.6 Batch analyses**

Certificates of analysis have been supplied for 8 batches, all of which comply with the specifications. These cover a period from 1995 to 2003 for a range of batch sizes. Additional data has been supplied for 38 batches, from 1991 to 2001, showing that the two main impurities are controlled.

## **2.7 Reference standards**

Relevant information on the reference standards has been supplied.

## **2.8 Container closure system**

The active substance is packed in suitable packaging.. Relevant specifications have been provided.

Relevant certification has been supplied regarding the compliance of the packaging with the EU requirements for food grade contact materials.

## **2.9 Stability**

Appropriate stability data have been generated. No significant deviations from initial values were noted for any of the parameters monitored (when presented within the degree of confidence allowed by the analytical methods as presented).

The data presented demonstrates a stable active substance and that the potential degradation pathways are understood. The manufacturer has recommended that the active substance be stored in the original package, however no shelf-life has been proposed. A retest period of five years has been set.

### 3. DRUG PRODUCT

#### 3.1 Composition

The qualitative composition of the tablets is summarised in table 4. The finished product is a hard gelatin capsule filled with retard pellets. The pellets contain 30mg of active substance. Only one type of pellet is used in the product.

**Table 4**

<b>Formulation</b>	<b>Function</b>	<b>Reference</b>
Propiverine hydrochloride	Active substance	In-house
Citric acid (anhydrous)	Starter crystals, pH adjuster	Ph. Eur.
Povidone	Binding agent	Ph. Eur.
Lactose monohydrate	Filler	Ph. Eur.
Talc	Lubricant	Ph. Eur.
Triethylcitrate	Plasticizer	Ph. Eur.
Magnesium stearate	Lubricant	Ph. Eur.
Methacrylic acid-methyl methacrylate copolymer (1:1)	Enteric coating material	Ph. Eur.
Methacrylic acid-methyl methacrylate copolymer (1:2)	Enteric coating material	Ph. Eur.
Ammonio methacrylate copolymer type A	Extended release coating material	Ph. Eur.
Ammonio methacrylate copolymer type B	Extended release coating material	Ph. Eur.
Acetone	Solvent	Ph. Eur.
Isopropyl alcohol	Solvent	Ph. Eur.
Purified water	Solvent	Ph. Eur.
<b>Total</b>		

The solvents are removed by drying from the finished product and are only present within the limits of the residual solvent specifications.

The hard gelatin capsule is size 3 with an orange cap and white body. The qualitative composition is summarised in table 5.

**Table 5**

<b>Ingredient</b>	<b>Function</b>	<b>Reference</b>
Gelatin	Capsule material	Ph. Eur.
Titanium dioxide E171	Colouring agent	Ph. Eur.
Red iron oxide E172	Colouring agent	95/45/EC

Yellow iron oxide E172		Colouring agent	95/45/EC
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### **3.2 Pharmaceutical Development**

The development pharmaceuticals were fairly well presented and the issues addressed, including the rationale for the formulation and its subsequent evolution. Development studies on packaging materials were provided. Chemical and physical compatibility were demonstrated in the course of the finished product stability studies.

### **3.3 Manufacture**

Manufacturer(s)

GMP certification from the authorities dated December 2004 and a manufacturer's licence dated March 2005 have been provided for the finished product manufacturer.

Batch formula

The batch formula for 360kg has been presented. This equates to 2250000 capsules containing 30mg propiverine hydrochloride or 1500000 capsules containing 45mg propiverine hydrochloride.

Details have been provided for the quantities used at each step of the manufacturing process.

Manufacturing process and process controls

A flow diagram detailing the manufacturing process has been provided. A written summary of the process is also included.

The manufacture of the product is relatively simple and uses conventional pharmaceutical methods. The account of the process is generally satisfactory.

It has been confirmed that the shelf-life of the finished product is set from the beginning of the manufacturing process when the active substance is first used in combination with the other ingredients in line with the guideline.

In-process controls

The in-process controls are suitable for this type of product and the limits are reasonable. Relevant details have been provided on the pharmacopoeia and non-pharmacopoeia methods used for the in-process controls.

A suitable sampling plan for all the in-process controls including quantities, locations and timings has been provided.

Control of critical steps and intermediates

Critical manufacturing steps have been identified. Acceptable tolerance ranges for each of these steps have been set for the relevant specifications.

The encapsulation step has also been identified as a critical step. However no specific parameter has been identified to be controlled, with further validation required.

The final blend and the bulk capsules have been identified as intermediates.

The finished pellets are controlled to suitable specifications. Relevant details of the methods have been provided. The bulk capsules are tested to suitable specifications. Relevant details of the test methods have been provided.

Process validation or evaluation

Validation batches were manufactured on the equipment intended for commercial manufacture and are essentially production scale.

The critical steps for validation have been identified and the relevant sampling schedule provided. The limits for the critical steps have been confirmed across the validation batches.

Acceptable storage time limits for the pellets and capsules have been proposed. All samples were stored in a GMP storage room (5°C to 25°C, humidity controlled) under the same storage conditions as the manufacturing process. The packaging materials are the same as used during the manufacturing process.

Post-approval validation commitment has been made for the first three production batches. Relevant details have been provided relating to the parameters to be tested and the sample to be taken.

### **3.4 Control of materials**

Control of excipients

Citric acid anhydrous, povidone K25, lactose monohydrate, talc, triethylcitrate, 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, 2-propanol and purified water all have monographs in the Ph. Eur.

Certificates of analysis have been supplied from the finished product manufacture for all the excipients except purified water and comply with the relevant monographs.

All excipients are tested according to the European Pharmacopoeia monograph.

Purified water is manufactured on site. Relevant details have been provided on the control tests performed and the relevant frequencies.

The gelatin capsule shell contains the colour ingredients titanium dioxide, red iron oxide and yellow iron oxide. Relevant certificates of analysis have been provided from the capsule manufacturer for the capsule and each of the colouring components. All of the colouring components comply with the purity requirements for food colours.

Relevant certification on BSE/TSE status has been provided for lactose monohydrate, methacrylic acid-methyl methacrylate copolymer (1:1 and 1:2) and ammonio methacrylate copolymer (types A and B). Certificates of suitability have been provided for the stearic acid used to manufacture the magnesium stearate and the gelatin. The certificates of suitability listed for the gelatin are Nitta Gelatin Inc R0-CEP 2000-085 and R0-CEP 2004-121, Rousselot SAS R1-CEP 2000-029 and R1-CEP 2000-027, Gelita Group R0-CEP 2003-028 and PB Gelatins R0-CEP 2002-126 and R0-CEP 2002-110.

#### Analytical methods

The relevant pharmacopoeia methods have been used.

#### Analytical method validation

Validation has not been deemed necessary as the methods used are those described in the pharmacopoeia.

### 3.5 Control of drug product

#### Specification

The finished product specifications for the capsules is satisfactory.

#### Analytical procedures

All the details have been provided for the pharmacopoeia and non-pharmacopoeia methods.

#### Validation

The process was appropriately validated. The data generated were generally consistent and complied with the control specification. The process appears to be under control and provides a reproducible bulk product equivalent to the clinical study batch.

#### Batch analyses

Batch analyses have been provided for the 7 clinical batches. All batches are within the relevant specifications at the time. There are differences in formulation across the 7 batches, including differences in active substance concentration. Only one clinical

batch corresponds to the proposed formulation. Additional supporting data has been presented in terms of the stability batches.

### **3.6 Container closure system**

The packaging consists of PVC/thermo elastomer (polyurethane)/PVdC-aluminium blister packs.

Compatibility with the finished product has been assumed on the basis of the stability.

For the packaging system relevant tests and specifications have been supplied. Certificates of conformity, relevant drawings and certification on suitability of contact materials have also been provided.

### **3.7 Stability**

Stability data have been provided for three batches packed into the polyethylene tubs (which have since been removed from the marketing authorisation) and the blisters. The samples were tested to suitable specifications.

A shelf-life of 36 months has been proposed with the following storage conditions: Store in the original container and Do not store above 25°C

On the basis of the data provided the proposed shelf-life is acceptable.

### **3.8 Other information**

#### Bioanalytical methods

No bioanalytical determination of the drug substance or its metabolites was performed.

#### Clinical studies

A range of clinical studies have been completed. See medical assessment for further details.

The batches used in the principle clinical study P659,1 have a batch size in excess of 50% of the intended maximum commercial batch size.

It has been confirmed that the reference product sourced from Germany is identical in terms of formulation and release specifications to the product available on the UK market, manufactured at the same facility under the same conditions.

#### Essential similarity

The active substance used in the finished product is the same source as that used in the reference product. No comparative dissolution data has been provided as a consequence of the formulation differences.

#### **4. PRODUCT LITERATURE**

##### **4.1 SPC**

The SPC is in compliance with the SPC guideline and quality section.

##### **4.2 PIL**

The PIL is in compliance with the SPC and relevant guidelines.

##### **4.3 LABEL**

The label is in compliance with the SPC and relevant guidelines.

#### **5. ADMINISTRATIVE**

##### **5.1 MAA form**

The MAA is in line with the SPC and relevant guidelines.

##### **5.2 Quality overall summary**

The quality report has been completed by a suitably qualified expert. The report is a summary of the module.

#### **6. CONCLUSIONS AND ADVICE**

A marketing authorisation can be granted.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are required for an application of this type.

## CLINICAL ASSESSMENT

This is a national application for the UK marketing authorisation, probably intended for subsequent mutual recognition by other Member States.

The applicant holds a marketing authorisation for an immediate release formulation of the active ingredient (propiverine hydrochloride) under the name Detrunorm 15mg Coated Tablets (PL 20072/0015).

The following propiverine-containing products have been approved in the UK:

PL	Name	MAH	Date
15072/0002  This went through MRP UK/H/271/01 Day 90: 20 Sept 1998	Mictonorm® 15 mg Coated Tablets	APOGEPHA Arzneimittel GmbH Kyffhäuserstraße 27 01309 Dresden Germany	23 April 1998
20072/0015	Detrunorm® 15 mg Coated Tablets	Amdipharm plc Regency House Miles Gray Road Basildon Essex SS14 3AF	15 July 2004

As a standard dose one coated tablet (= 15 mg propiverine hydrochloride) twice a day is recommended. This may be increased to three times a day. Some patients may already respond to a dosage of 15 mg a day. For neurogenic detrusor overactivity a dose of one coated tablet three times a day is recommended. This may be increased to four times a day if necessary and tolerated (maximum recommended daily dose).

The application under assessment at present is a line extension for a new strength/modified release preparation.

The clinical expert for the applicant is suitably qualified.

### **1. Introduction**

This product contains 30 mg propiverine hydrochloride, equivalent to 27.28 mg propiverine per capsule, in a modified release formulation.

Propiverine is indicated for the treatment of urinary incontinence, as well as urgency and frequency in patients who have idiopathic detrusor overactivity (overactive bladder).

The recommended daily dose of the product under assessment is as follows:

#### **Adults:**

As a standard dose one capsule once a day is recommended.

Elderly:

Generally there is no special dosage regimen for the elderly.

Pharmacology of propiverine

Propiverine is claimed to act by inhibition of calcium influx and modulation of intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis. It also inhibits the efferent connection of the nervus pelvici due to anticholinergic action.

In animal models propiverine hydrochloride causes a dose-dependent decrease of 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.

Propiverine is extensively metabolised by intestinal and hepatic enzymes. The primary metabolic route involves the oxidation of 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 N-oxide greatly exceeds that of the parent substance. Four metabolites have been identified in urine - three of them are pharmacologically active and may contribute to 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.

Food intake increases the bioavailability of propiverine (mean increase 1.3-fold) when administered as immediate release coated tablets. 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. 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. The comparison of trough plasma concentrations during steady state revealed no difference between older patients and young healthy subjects.

The applicant has submitted 31 volumes of Module 5 data, which includes the following clinical studies:

<b>Study</b>	<b>Objective</b>
P 387	Relative intestinal bioavailability
P 426	Relative bioavailability of 3 pellet formulations of propiverine
P 506.1	Bioequivalence of propiverine ER and IR
P 701	Dose proportionality of 4 single doses of 10mg, 15mg, 30mg and 45mg of ER capsules
P 702	To establish a point-to-point in vitro/in vivo correlation by means of 3 extended release formulations differing in their in vitro dissolution
P 703	Food interaction study with propiverine ER and IR
P 659.1	Clinical efficacy and safety study comparing IR (n = 395 patients) and ER (n = 391 patients) with placebo (n = 202 patients)

## **2. Assessment**

### **2.1 Product name**

The name of the index product under assessment “Detrunorm XL 30mg Capsules” raised some concern as there is another product by the name of “Detrusitol XL” (also capsules) already approved in the UK (PL 00320287) to Pharmacia Ltd, Sandwich, Kent. It contains tolterodine tartrate 40mg and is also indicated for urinary incontinence.

Both are indicated once daily but the two drug substances have different safety profiles, most especially their drug interaction profiles. Given that the majority of the target population are elderly, who are in receipt of polypharmacy, this raised some concern.

However, following discussions with MHRA staff, it was concluded that the risk appears to be theoretical rather than real. The Agency has allowed these names previously and there is no evidence that these have proved to be a risk. Given that this new formulation will be subject to special ADR monitoring, it was decided not raise the issue of name at present.

### **2.2. Therapeutic indications**

Immediate release formulations have been approved for:

“The treatment of urinary incontinence, as well as urgency and frequency in patients who have either idiopathic detrusor overactivity (overactive bladder) or neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord injuries, e.g. transverse lesion paraplegia.”

Extended release formulations are intended for:

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

The therapeutic indications are, therefore, acceptable.

### **2.3. Posology and method of administration**

Immediate release formulations:

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

For neurogenic detrusor overactivity a dose of one coated tablet three times a day is recommended. This may be increased to four times a day if necessary and tolerated (maximum recommended daily dose).

There is no clinically relevant effect of food on the pharmacokinetics of propiverine. Accordingly, there is no particular recommendation for the intake of propiverine in relation to food.

This medicinal product contains 0.61 mg of glucose. Accordingly, a daily dose of 2 coated tablets supplies 1.22 mg of glucose.

Extended release formulations:

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

There is no clinically relevant effect of food on the pharmacokinetics of propiverine. Accordingly, there is no particular recommendation for the intake of propiverine in relation to food.

The recommended posology and method of administration are, therefore, acceptable.

#### 2.4. Contraindications

Identical.

Apart from the following statement that has been added to this section:

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

#### 2.5. Special warnings and precautions for use

Apart from omission of the warning related to the presence of cochineal red A (E124, lake), which is present in the SPC of the immediate release formulation (Cochineal red A may cause allergic reactions), the rest of the details are identical apart from the following statement that was added because the extended release formulation contains lactose monohydrate:

“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.”

#### 2.6. Interactions with other medicinal products and other forms of interaction

Identical

#### 2.7. Pregnancy and lactation

The SPC for the immediate release formulations states:

There are no adequate data from the use of propiverine hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

The drug is secreted into the milk of lactating mammals.

Propiverine hydrochloride should not be used during pregnancy and should not be administered to nursing women.

The SPC proposed for extended release products under assessment states:

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.

The instructions for pregnant and lactating women are, therefore, acceptable.

#### 2.8. Effects on ability to drive and use machines

Identical

#### 2.9. Undesirable effects

Identical

#### 2.10. Overdose

Identical

#### 2.11. Pharmacodynamic properties

Identical

#### 2.12 Pharmacokinetic properties

This section has been modified as appropriate to the extended release formulation.

### **3. Biopharmaceutics**

Of the six biopharmaceutical studies, the following three phase 1 studies are not directly relevant to clinical safety and efficacy and are not discussed in this Assessment Report:

P 387	Relative intestinal bioavailability in 4 healthy volunteers
P 426	Relative bioavailability of 3 pellet formulations of propiverine in 6 healthy volunteers
P 702	To establish a point-to-point in vitro/in vivo correlation by means of 3 extended release formulations differing in their in vitro dissolution in 12 healthy volunteers

The following three studies are directly relevant and the results from these are summarised below:

<b>Study</b>	<b>Objective</b>
P 506.1	Bioequivalence of propiverine ER and IR in 24 healthy volunteers
P 701	Dose proportionality of 4 single doses of 10mg, 15mg, 30mg and 45mg of ER capsules in 10 healthy volunteers

P 703	Food interaction study with propiverine ER and IR in 24 healthy volunteers
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### 3.1 P 506.1 - Bioequivalence of propiverine ER and IR

This multiple dose study in 24 healthy volunteers compared the equivalence of 15mg three times daily of immediate release formulation (Mictonorm) with a 45mg once daily of extended release formulation.

Design: Controlled, randomised, double-blind, double dummy, 2-period cross over study

Duration of each treatment: 7 days

Washout period: 14 days

#### **Results:**

The geometric means of the following PK-parameters for Propiverine were compared (test vs. reference):

AUC(0-24), Cave, Cmax, Cmin, Peak-trough fluctuation, Half-life, CL(renal), CL(metabolic), Ae ( $\mu\text{g}$ )

For its main metabolite Propiverine-N-oxide:  
AUC(0-24), Cave, Cmax, Cmin, Peak-trough fluctuation.

There was no relevant difference between Test- and Reference-Pharmacokinetics.

**Conclusion:** *This study shows that the two treatments are equivalent in terms of the extent of absorption.*

*More detailed exploratory analysis showed that the fluctuations of the steady state concentrations during once daily administration of the extended release formulation given once daily were not larger than those observed after administration of the immediate release formulation given thrice daily.*

*The metabolite profile shows a much greater variability but this may reflect the rates of metabolism of the parent drug. In any case, the contribution of the metabolite to the therapeutic effect is unremarkable.*

### 3.2 P 701 - Dose proportionality study

Single dose, controlled, randomised, double-blind, 5-treatment period cross over study in 10 healthy volunteers

Treatments: 1 capsule of 10mg extended release formulation  
1 capsule of 15mg extended release formulation  
1 capsule of 30mg extended release formulation  
1 capsule of 45mg extended release formulation  
5ml intravenous solution of propiverine (3mg/ml)

Blood sampling: 96 hours after oral administration  
72 hours after intravenous administration

### **Results:**

The geometric means of PK-parameters for Propiverine, AUC(0- $\alpha$ ), C<sub>max</sub>, T<sub>max</sub>, F, Half-life, CL to N-oxide and AUC(0- $\alpha$ ), C<sub>max</sub> (Normalised to a dose of 15mg) and for Propiverine\_N-oxide AUC(0- $\alpha$ ), C<sub>max</sub>, T<sub>max</sub>, Half-life, and AUC(0- $\alpha$ ), C<sub>max</sub> (Normalised to a dose of 15mg) revealed an increase proportional to the dose administered.

**Conclusion:** *This study establishes the dose proportionality of extended release formulation in the range of 10mg to 45 mg.*

### 3.3 P 703 - Food interaction study with propiverine ER and IR

Randomised, open, 4-way cross over study in 24 healthy volunteers

Treatments: Single oral doses

- 15mg x 2 tablets of immediate release formulation (Mictonorm)
- With food and when fasting
- 45 mg x 1 capsule of extended release formulation
- With food and when fasting

Blood sampling: 72 hours post dose for immediate release formulation  
96 hours post dose for extended release formulation

Urine samples: For periods 0-3 h, 3.6 h, 6-12 h, 12-24 h, 24-48 h and 48-72 h after dosing.

### **Results:**

#### ***Immediate release formulation:***

The pharmacokinetics are in accordance to the SmPC for Detrunorm 15 mg (PL 20072/0015)

#### ***Extended release formulation:***

The results of the pharmacokinetic evaluation of Propiverine profiles following the extended release capsule under fasting conditions and after meal clearly indicate no relevant difference. Mean C<sub>max</sub> values differ by 3% with identical mean t<sub>max</sub> values.

AUC values are nearly identical for both treatments. All 90% confidence intervals are within the acceptance ranges.

Administration of the ER capsule after meal lead to higher peak concentrations of the main metabolite,

Propiverine-N-oxide, ( $f=1.26$ ). The corresponding 90% confidence interval, however, was completely

inside the acceptance range. The AUC values were nearly identical for both treatments with 90%

confidence intervals, completely within the acceptance range.

**Conclusion:** *There is NO food-drug interaction with extended release formulation.*

## **4. Clinical study on safety and efficacy**

### **4.1 P 659.1 - Clinical efficacy and safety study**

#### ***Study:***

The primary objective of this study was to compare the safety and efficacy of extended and immediate release formulations of propiverine with placebo.

Double-blind, double dummy, randomised, placebo-controlled parallel groups, multicentre study.

After a run-in period of 7 days, patients were randomised to receive placebo, propiverine 30mg ER capsule or propiverine IR (Mictonorm 15mg BD) for 32 days.

There were 4 evaluation visits during the trial:

Visit 1	Days -7 to -1
Visit 2	Day 0
Visit 3	Day 28 +3
Visit 4	Day 32 +3

Primary efficacy criteria: Number of incontinence episodes within 24 hours

Secondary endpoints: Number of micturitions within 24 hours

Number of urge episodes within 24 hours

for 3 consecutive days during screening period (days -6 to -1) and at the end of treatment phase (days 29 to 31).

Other secondary endpoints were volume of micturition documented for at least 1 day during screening (days -6 to -1) and the end of treatment phase (days 29 to 31).

The primary efficacy variable was evaluated with an a priori hypothesis to test for non-inferiority of ER to IR formulations, as well as to show superiority of both formulations over placebo.

No exact sample size calculation was considered possible due to lack of sufficient database on which to do this calculation. Therefore, as described by Bauer and Kohne (1994), an adaptive interim analysis was performed to re-calculate the sample size.

An interim analysis was performed after cohort I of 189 patients had completed the study and a final analysis after another cohort II of 799 patients had completed the study, making a total of 988 patients for pooled analysis. Thus, cohort I included 19% of the ultimate pooled cohort.

About 90% of the patients were females and 99.9% were Caucasians.

The three groups were comparable in age distribution and in all other respects as well.

***Patient disposition:***

Pooled analysis (Cohort I and II)

	IR	ER	Placebo	Total
Enrolled	395	391	202	988
Randomised	395	391	202	988
Completed study				
Visit 3	374	373	195	942
Visit 4	374	372	194	940
End	369	368	191	928
Reasons for discontinuation	6.6%	5.9%	5.4%	6.1%
Adverse event	15	10	1	26
Loss to follow up	5	3	3	11
Protocol violations	2	2	-	4
Insufficient efficacy	-	1	2	3
Other reasons	4	7	5	16
Total	26	23	11	60

Cohort II shown below consisted of 799 patients who were all randomised at visit 2

	IR	ER	Placebo	Total
Enrolled	318	318	163	799
Randomised	318	318	163	799
Completed study				
Visit 3	300	303	157	760
Visit 4	300	303	156	759
End	297	299	153	749
Reasons for discontinuation	6.6%	6.0%	6.1%	6.3%
Adverse event	13	10	1	24
Loss to follow up	3	2	2	7
Protocol violations	1	2	-	3
Insufficient efficacy	-	-	2	2
Other reasons	4	5	5	14
Total	21	19	10	50

It is evident that cohort II is representative of the whole pooled population.

***Dataset analysed:***

Cohort II of 799 patients:

	IR	ER	Placebo	Total
N	318	318	163	799
Safety population	318	318	163	799
ITT	315	311	160	786
Per protocol	290	294	151	735
Modified Per protocol population	282	287	143	712

Cohort I + II of 988 patients:

	IR	ER	Placebo	Total
N	395	391	202	988
Safety population	395	391	202	988
ITT	391	384	199	974
Per protocol	360	363	187	910

***Results on primary efficacy variable*** (number of incontinence episodes):

The overall confirmatory analysis was statistically significant (1-sided  $p < 0.0038$ ) for all tests. The p-value for the non-inferiority of propiverine IR versus propiverine ER was  $p < 0.0001$ , the p-value for superiority of propiverine IR over placebo was  $p = 0.0001$ , and p-value for superiority of propiverine ER over placebo was  $p < 0.0001$ . The results of the parametric tests were confirmed by sensitivity analyses with non-parametric tests ( $p < 0.0001$ ). Propiverine extended release is more effective than placebo for the treatment of urge urinary incontinence. Propiverine ER is not inferior to propiverine IR.

The results of ***the secondary endpoints of efficacy*** were in line with the results of the primary efficacy variable for almost all the comparisons.

- the number of micturitions within 24 hours was statistically significantly more reduced in both propiverine groups than in the placebo group but the difference between the two propiverine groups was not statistically significant
- the number of urge episodes within 24 hours was statistically significantly more reduced in both propiverine groups than in the placebo group but the difference between the two propiverine groups was not statistically significant
- the mean volume of the single micturitions was statistically significantly more increased in both propiverine groups than in the placebo group but the difference between the two propiverine groups was not statistically significant

***Safety:***

	IR N = 395	ER N = 391	Placebo N = 202
Number of treatment emergent adverse events (TEAE)	279	246	58
% of patients with at least 1 TEAE	38.5% n = 152	34.3% n = 134	20.3% n = 41
% of patients with at least 1 severe TEAE	3.8%	2.8%	0
% of patients with at least 1 serious TEAE	0	0.3%	0
% of patients dropping out due to TEAE	3.5%	2.8%	0.5%

% Incidence of adverse events by SOC most affected:

	IR N = 395	ER N = 391	Placebo N = 202
Total	152 = 38.5%	134 = 34.3%	41 = 20.3%
Gastro-intestinal	27.8	25.8	8.9
Eyes	6.6	7.2	2.5
Nervous system	4.8	4.9	2.5
Infections etc	1.8	3.1	2.0
General disorders	2.3	1.0	1.0

% Incidence of most frequent adverse events:

	IR N = 395	ER N = 391	Placebo N = 202
Total	152 = 38.5%	134 = 34.3%	41 = 20.3%
Dry mouth	22.8	21.7	6.4
Blurred vision	3.8	4.6	0.5
(aggravated) Constipation	3.8	3.3	1.0
Abdominal pain	2.8	1.8	0
Nausea	2.5	1.5	1.0
Headache	2.0	1.5	0.5
Accommodation disorder	2.0	0.8	1.5
Dizziness	1.0	1.5	0.5
Dysgeusia	0.8	1.5	0
Dyspepsia	1.3	0.8	0.5

Intensity and causality of adverse events:

	IR N = 395	ER N = 391	Placebo N = 202
Total	152 = 38.5%	134 = 34.3%	41 = 20.3%
Mild	24.3 %	22.3 %	16.3 %
Moderate	10.4 %	9.2 %	4.0 %

Severe	3.8 %	2.8 %	0
Related	33.4%	29.9%	14.9%

The laboratory safety profile and effects on vital signs were unremarkable. The comparisons between the two formulations of propiverine were unremarkable.

ECGs were recorded at visits 1 and 3. There were no remarkable changes in these ECGs. There were 7 patients whose ECGs revealed clinically relevant ECG changes:

4 on IR: LVH, mild tachycardia, LBBB and QRS prolongation,  
Old infarction

1 on ER: Ventricular premature beat and later sustained bigeminy

2 on placebo: LVH and LVH

Frequently, these changes were also present at baseline

There were no changes in PR interval, QRS interval or QTc interval corrected by Bazett. None of the ECGs showed the categorical responses in QTc interval as described in the CPMP Points to Consider document.

### **Assessor's conclusion on efficacy and safety:**

The two formulations are comparable in terms of safety and efficacy – if anything, the extended release formulation has a marginal advantage.

## **5. Conclusions**

The applicant has undertaken a very satisfactory programme for the development of an extended release formulation of this higher strength product.

Bioequivalence between the immediate release and extended release formulations has been established and, if anything, the extended release formulation has a better pharmacokinetic profile.

The data on biopharmaceutics have been supplemented by additional clinical efficacy and safety data that are also satisfactory. In principle, therefore, the extended release preparation is approvable.

The name of the index product under assessment “Detrunorm XL 30mg Capsules” was considered a potential cause for concern. There is another product by the name of “Detrusitol XL” (also capsules) already approved in the UK (PL 00320287) to Pharmacia Ltd, Sandwich, Kent, UK. It contains tolterodine tartrate 4mg and is also indicated for urinary incontinence. Both are indicated once daily but the two drug substances have different safety profiles, most especially their drug interaction profile. Given that the majority of the target population are elderly who are in receipt of polypharmacy, the risk of drug interactions had to be considered.

However, following discussions with the MHRA staff, it was concluded that the risk appears to be theoretical rather than real. The Agency has allowed these names before and there is no evidence that these have proved to be a risk. Given that this new formulation will be subject to special ADR monitoring, it was decided not raise the issue of name at present.

The SPC for the extended release preparation is satisfactory.

## **6. Recommendations**

There are no major clinical public health issues and the recommendation is to grant a marketing authorisation for this preparation.

## **OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Detrunorm XL 30 mg Modified Release Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### **PRECLINICAL**

No new preclinical data were submitted and none are required for applications of this type.

### **EFFICACY**

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the cross-reference product.

### **RISK BENEFIT ASSESSMENT**

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and some benefit has been shown to be associated with Detrunorm XL 30 mg Modified Release Capsules. The risk benefit is therefore considered to be positive.

## DETRUNORM XL 30MG MODIFIED RELEASE CAPSULES

PL 20072/0016

### STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 6 September 2004
2	Following assessment of the application the MHRA requested further information relating to the quality dossier on 25 April 2005 and the clinical dossier on 31 August 2005
3	The applicant responded to the MHRA's requests, providing further information on the quality dossier 21 October 2005 and the clinical dossier on 17 November 2005
4	Following assessment of the application the MHRA requested further information relating to the quality dossier on 8 December 2005
5	The applicant responded to the MHRA's requests, providing further information on 9 December 2005
6	Following assessment of the response the MHRA requested further additional information relating to the quality dossier on 9 December 2005
7	The applicant responded to the MHRA's requests, providing further information on 24 January 2006
8	Following assessment of the response the MHRA requested further additional information relating to the quality dossier on 24 January 2006
9	The applicant responded to the MHRA's requests, providing further information on 16 March 2006
10	The application was determined on 3 April 2006

**Product Summary for Detrunorm XL 30mg Modified Release Capsules (PL 20072/0016):**

**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 asazole 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)
<b>Very common (&gt;1/10)</b> - dry mouth	Gastrointestinal
<b>Common (&gt;1/100, &lt;1/10)</b> - accommodation abnormal, accommodation disturbances, vision abnormal	Eye
- constipation	Gastrointestinal
<b>Adverse reactions</b>	<b>System organ class (Disorders</b>

	according to MedDRA)
<b>Uncommon (&gt;1/1,000, &lt;1/100)</b>	
- 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
<b>Rare (&gt;1/10,000, &lt;1/1,000)</b>	
- rash due to idiosyncrasy (propiverine hydrochloride) or hypersensitivity (excipients, e.g. colorant)	Skin and subcutaneous tissue
<b>Very rare (&lt;1/10,000, including isolated reports)</b>	
- palpitation	Cardiac
- restlessness, confusion	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).

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 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 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 ( $C_{average} = 71$  ng/ml).

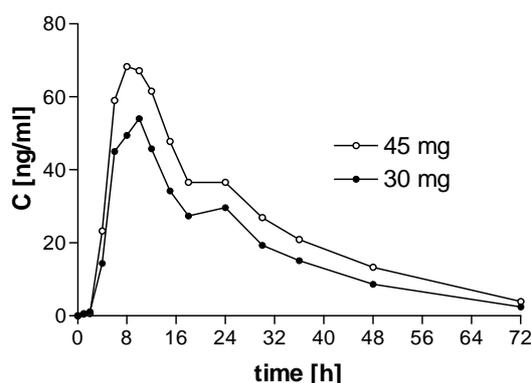
The volume of distribution was estimated in 21 healthy volunteers after intravenous administration of propiverine hydrochloride to range from 125 to 473 l (mean 279 l) indicating, that a large amount of available propiverine is

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,  $\pm$  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 <sub>0-∞</sub> [ng·h/ml]	1378 (903, 2104)	1909 (1002, 3639)
C <sub>max</sub> [ng/ml]	60.6 (41.5, 88.6)	80.0 (41.8, 152.1)
t <sub>1/2</sub> [h]	14.2 (10.8, 18.6)	16.3 (13.9, 19.2)
t <sub>max</sub> [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:

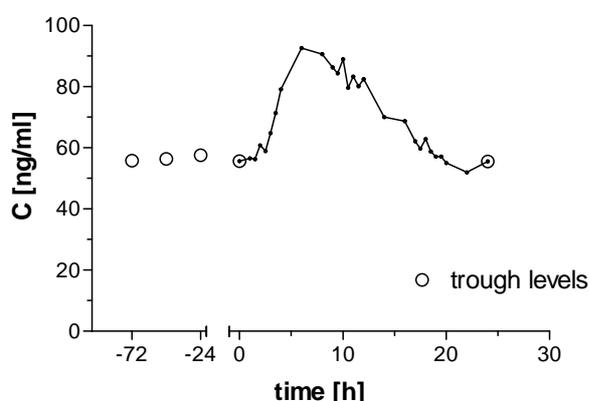


Steady state characteristics of propiverine following multiple-dose administration to 24 healthy volunteers of propiverine hydrochloride modified release capsules 45 mg once daily for 7 days:

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

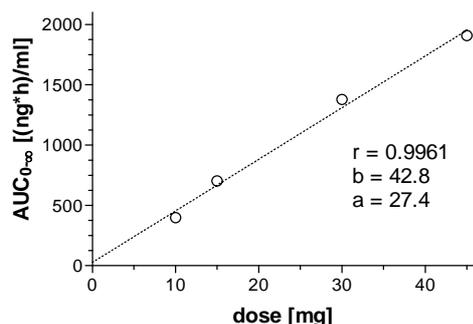
### **Elimination**

Following administration of 30 mg oral dose of <sup>14</sup>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).

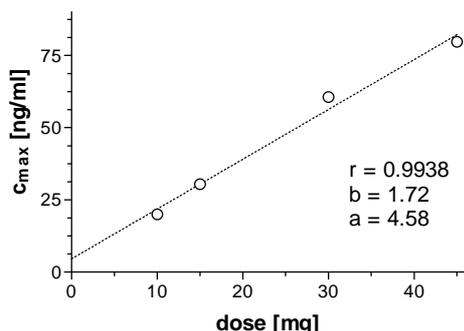
### **Linearity/non-linearity**

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  $AUC_{0-\infty}$ :



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  
Regency House  
Miles Gray Road  
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

03/04/2006

**PATIENT INFORMATION LEAFLET**

ORIGINATED FOR:	AMDIPHARM	OFFICIAL ARTWORK PROOF PRODUCED BY MANDEVILLE PRESS LTD	BARCODE NO.:		
DATE PROOFED:	31-01-06		PRODUCT REF:	751-1223	
SCALE:	100%	PRODUCT NAME:	DETRUNORM XL PIL	COLOUR PAN:	BLACK
(RE-PROOF):		ORIGINATED ON:	10-08-05	COLOUR PAN:	
(OK TO RUN):		VERSION:	10	COLOUR PAN:	
DATE REQUIRED:	ASAP	DIE TYPE & NO.:	180 X 300	COLOUR PAN:	

751-1223

PATIENT INFORMATION LEAFLET



AMDIPHARM

## DETRUNORM<sup>®</sup> XL 30 mg Modified Release Capsules

Propiverine hydrochloride

**Read all of this leaflet carefully before you start taking this medicine.**

Keep this leaflet. You may need to read it again.

If you have any further questions, please ask your doctor or your pharmacist.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**In this leaflet:**

1. What your medicine is and what it is used for
2. Before you take your medicine
3. How to take your medicine
4. Possible side effects
5. Looking after your medicine

### 1. What your medicine is and what it is used for

The name of your medicine is Detrunorm XL 30 mg Modified Release Capsules.

Each modified release capsule contains 30 mg of the active ingredient propiverine hydrochloride (equivalent to 27.28 mg propiverine), along with the following inactive ingredients: citric acid, povidone, lactose monohydrate, talc, triethyl citrate, magnesium stearate, methacrylic acid-methyl methacrylate copolymer, ammonio methacrylate copolymer, gelatin, titanium dioxide (E171), red iron oxide (E172) and yellow iron oxide (E172).

**The Marketing Authorisation Holder is:**

Amdipharm Plc, Regency House, Miles Gray Road, Basildon, Essex SS14 3AF

**The manufacturer responsible for release is:**

Amdipharm Plc, Regency House, Miles Gray Road, Basildon, Essex SS14 3AF

Detrunorm XL 30 mg Modified Release Capsules are orange and white capsules. They are available in blister packs containing 14, 20, 28, 30, 49, 50, 56, 60, 98, 100 or 112 capsules. (Only marketed pack types and sizes will be shown on the final printed leaflet)

**What type of medicine is it?**

Propiverine hydrochloride is one of a group of medicines called anticholinergics. They increase the capacity of the bladder by interfering with the process that causes the bladder to contract.

**What are Detrunorm XL 30 mg Modified Release Capsules used for?**

Detrunorm XL 30 mg Modified Release Capsules are for the treatment of some people who have difficulty in controlling their bladder due to bladder overactivity. Detrunorm XL 30 mg Modified Release Capsules can be used to treat the symptoms and is formulated as a modified release capsule to be taken once a day.

### 2. Before you take your medicine

**You should not take your medicine, but tell your doctor first if:**

- you have ever had an allergic reaction to Detrunorm XL 30 mg Modified Release Capsules or any of its ingredients
- you are pregnant or breast feeding
- you are suffering from any of the following conditions:
  - obstruction of the bowel
  - obstruction of the bladder causing difficulty in passing urine
  - myasthenia gravis (a muscle weakness)
  - intestinal paralysis
  - severe ulcerative colitis
  - toxic megacolon (fever, pain and tenderness of the abdomen)
  - uncontrolled angle closure glaucoma
  - moderate or severe liver disease
  - fast and irregular heart beat.

**Make sure your doctor knows if you have any of the following:**

- paralysis of part of the nervous system
- severe kidney disease
- heart failure, fast or irregular heart beat
- enlargement of the prostate gland
- hiatus hernia with reflux oesophagitis (heartburn and indigestion due to back flow of acid into the food pipe).

**If you become pregnant or you are breast-feeding**

You should tell your doctor as soon as possible if you are pregnant, you become pregnant or you are breast-feeding.

**Driving and operating machinery**

Detrunorm XL 30 mg Modified Release Capsules can sometimes cause drowsiness and blurred vision. You should not drive or operate machinery until you are sure you are not affected.

**Important information about one of the ingredients of your medicine**

This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

**Taking other medicines**

Make sure you tell your doctor if you are taking any other type of medicine, such as:

- antidepressants (e.g. imipramine)
- sedatives (e.g. benzodiazepines)
- anticholinergics (usually used to treat asthma, stomach cramps, eye problems or urinary incontinence)
- amantadine (used to treat Parkinson's disease)
- phenothiazines (usually used to treat hay fever, nausea and vomiting, difficulty in sleeping, anxiety)
- $\beta$ -sympathomimetics (usually used to treat asthma, heart conditions, eye problems, blocked noses)
- isoniazid (used to treat tuberculosis)
- metoclopramide (used to prevent nausea and vomiting)
- cisapride (used to treat heartburn)

as the effect of these may be altered by use of Detrunorm XL 30 mg Modified Release Capsules. If you are not sure, ask your doctor or pharmacist.

If you receive long term treatment with Detrunorm XL 30 mg Modified Release Capsules it may be necessary for your doctor to occasionally test your liver enzymes.

If you are at risk of developing glaucoma, your doctor may check your eyes while you are being treated with Detrunorm XL 30mg Modified Release Capsules.

**3. How to take your medicine**

Detrunorm XL 30 mg Modified Release Capsules are for oral use.

*Adults and elderly patients:* one modified release capsule to be swallowed once a day.

Always follow your doctor's advice. Do not take the capsules more often than you are told to. Do not crush or chew the capsules.

Detrunorm XL 30 mg Modified Release Capsules can be taken with or without food.

**THESE CAPSULES ARE NOT RECOMMENDED FOR CHILDREN.**

**If you take more capsules than you should**

If you, or anybody else, accidentally take more capsules than you were told, you should report to the hospital immediately. Do not forget to take the medicine container with you so that the doctors can identify what has been taken.

**If you forget to take your capsule**

If you forget to take your capsule, take your recommended dose as soon as you remember, unless it is nearly time for the next dose, then carry on as before. Do not take a double dose to make up for the one you have missed.

**4. Possible side effects**

Most people do not have any problems whilst they are taking Detrunorm XL 30 mg Modified Release Capsules, but as with all medicines, the capsules can cause unwanted side effects in some patients.

Some people may find that they suffer from dryness of the mouth and also blurred vision, tiredness, headache, stomach pain and constipation. A few people may also suffer from an upset stomach, decreased blood pressure and drowsiness, dizziness, shaking, flushing of the face and neck, changes in taste and a slight problem passing urine.

Rarely, some people may also suffer an allergic reaction, restlessness, confusion and a fast or irregular heartbeat.

These side effects will pass and will stop altogether within 1 to 4 days after having your dose reduced, or if you stop taking the capsules. If you are worried by these or any other effects, you should tell your doctor or pharmacist.

In theory it is possible that you might suffer an acute attack of glaucoma. If you have been seeing coloured rings around lights or if you should develop severe pain in and around either eye you should seek medical attention urgently.

**5. Looking after your medicine**

Do not store the blister pack above 25°C.

Keep the blisters in the original package or keep the bottle tightly closed to protect from moisture.

Do not use after the expiry date printed on the carton.

**As with all medicines, keep out of the reach and sight of children.**

This leaflet does not contain all the available information about your medicine. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

This information in this leaflet applies only to Detrunorm XL 30 mg Modified Release Capsules.

Detrunorm is a registered trademark.

Date of preparation: December 2005



# LABELLING

## Carton:

Detrunorm XL AMDIPHARM 28 capsules BlackPantone 2597 CPantone 485 CPantone 293 Cpunch/stamp



punch 34 x 42 x 102

creation date: 04.01.06, 9.30 Uhr

**Blister:**

ORIGINATED FOR:	<b>AMDIPHARM</b>	<b>OFFICIAL ARTWORK PROOF PRODUCED BY MANDEVILLE PRESS LTD</b>	BAR CODE NO:	<b>50 60064</b>	
DATE PROOFED:	<b>31-01-06</b>		PRODUCT REF:	<b>797-</b>	
SCALE:	<b>100%</b>	PRODUCT NAME:	<b>DETRUNORM 30MG</b>	COLOUR PAN:	<b>PANTONE 2597</b>
(RE-PROOF):	<b>Edited at Waymade: 31-01-06</b>	ORIGINATED ON:	<b>17-01-05</b>	COLOUR PAN:	
(OK TO RUN)		VERSION:	<b>W1</b>	COLOUR PAN:	
DATE REQUIRED:	<b>ASAP</b>	DIE TYPE & NO.:	<b>A 98 X B 38</b>	COLOUR PAN:	

**Note: Batch number and expiry date to be overprinted at the time of packaging.**

