Public Assessment Report

Mutual Recognition Procedure

Mictonorm XL 45 mg Modified Release Capsules
(propiverine hydrochloride)

PL 15072/0010

UK/H/4594/001/MR

Apogepha Arzneimittel GmbH
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted APOGEPHA Arzneimittel GmbH Limited a Marketing Authorisation (licence) for the medicinal product Mictonorm XL 45 mg Modified Release Capsules (PL 15072/0010) in the UK on 30 November 2009.

On 9 March 2011 a Mutual Recognition Procedure for this medicinal product was initiated, with the UK acting as Reference Member State (RMS). The procedure concluded on 7 June 2011 with Marketing Authorisations for Mictonorm XL 45 mg Modified Release Capsules being granted in the Concerned Member States (CMS) Austria, Belgium, Czech Republic, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Slovenia and Slovakia.

This is a prescription only medicine (POM) and used for the treatment of people who have difficulty in controlling their bladders due to bladder overactivity or who have problems with the spinal cord.

Mictonorm XL contains the active substance propiverine hydrochloride. This substance prevents the bladder from contracting and increases the amount that the bladder can hold. Mictonorm XL is used to treat the symptoms of overactive bladder. It is a modified-release capsule that needs to be taken once a day.

The data submitted in support of the application for Mictonorm XL 45 mg 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 a Marketing Authorisation has been granted.
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### Module 1

**Information about Mutual Recognition Procedure**

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<th><strong>Name of the product in the Reference Member State</strong></th>
<th>Mictonorm XL 45 mg Modified-Release Capsules</th>
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<td><strong>Type of application</strong></td>
<td>Line extension</td>
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<tr>
<td><strong>Name of the active substance</strong></td>
<td>Propiverine hydrochloride</td>
</tr>
<tr>
<td><strong>Pharmacotherapeutic classification (ATC code)</strong></td>
<td>G04B D06 – urinary antispasmodics</td>
</tr>
<tr>
<td><strong>Pharmaceutical form and strength</strong></td>
<td>Modified-release capsule, hard 45mg</td>
</tr>
<tr>
<td><strong>Reference number for the Mutual Recognition Procedure</strong></td>
<td>UK/H/4594/01/MR</td>
</tr>
<tr>
<td><strong>Reference Member State</strong></td>
<td>United Kingdom</td>
</tr>
<tr>
<td><strong>Member States concerned</strong></td>
<td>Austria, Belgium, Czech Republic, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Slovenia and Slovakia</td>
</tr>
<tr>
<td><strong>Start date of Mutual Recognition Procedure</strong></td>
<td>9 March 2011</td>
</tr>
<tr>
<td><strong>End date of Mutual Recognition Procedure</strong></td>
<td>7 June 2011</td>
</tr>
<tr>
<td><strong>Marketing Authorisation number</strong></td>
<td>PL 15072/0010</td>
</tr>
<tr>
<td><strong>Name and address of the authorisation holder</strong></td>
<td>APOGEPHA Arzneimittel GmbH Kyffhäuserstraße 27, 01309 Dresden, Germany</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SPC) for Mictonorm XL 45 mg Modified Release Capsules is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Mictonorm XL 45 mg Modified-Release Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).
Excipients: Lactose monohydrate (8.5 mg),

for a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Modified-release capsule, hard
Orange size 2 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 in patients with overactive bladder syndrome or neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord injuries.

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: One capsule (= 45 mg propiverine hydrochloride) once daily.
As a standard treatment, one modified-release capsule 30 mg propiverine once a day or one 15 mg tablet of propiverine twice a day is recommended, this may be increased to one 15 mg tablet three times daily. Some patients may already respond to a dosage of 15 mg a day.
In patients whom propiverine 15 mg tablet three times daily is indicated, the 15 mg tablet three times daily regimen could be replaced by Mictonorm XL 45 mg Modified-Release Capsules once a day.

The maximum daily dose is one Mictonorm XL 45 mg Modified-Release Capsule daily.

Elderly: Generally there is no special dosage 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 clinicians should monitor patients carefully for side effects in the following dispositions (see sections 4.4, 4.5, 5.2).

Use in renal impairment
In the treatment of this group of patients caution has to be exercised. In patients with severe renal impairment (creatinine clearance < 30 ml/min) the maximum daily dose of propiverine is 30 mg. Therefore, Mictonorm XL 45 mg Modified-Release Capsules is not recommended in patients with severe renal failure.

Use in hepatic impairment
In patients with mild impaired hepatic function there is no need for a dose adjustment but caution should be exercised. The treatment of patients with moderate to severe impairment is not recommended because no data are available (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 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 be titrated to a higher dose. However, caution should be exercised and
clinicians should monitor these patients carefully for side effects (see sections 4.4, 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
- severe renal 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 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.
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 interaction
Increased effects due to concomitant medication with tricyclic antidepressants (e.g. imipramine), tranquilisers (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 **Fertility, pregnancy and lactation**
No effects on male and female fertility and reproduction behaviour were observed in toxicological studies with rats.

There are no data from the use of propiverine hydrochloride in pregnant woman. 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. A risk to the newborns cannot be excluded.

Propiverine hydrochloride is not recommended during pregnancy and should not be used during breast-feeding.

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 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**
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).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

- **Psychiatric disorders**
  - Very rare: restlessness, confusion
  - Not known: hallucination

- **Nervous system disorders**
  - Common: headache
  - Uncommon: tremor, dizziness, dysgeusia

- **Eye disorders**
  - Common: abnormal accommodation, accommodation disturbances, abnormal vision

- **Cardiac disorders**
  - 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**
  - Rare: rash due to idiosyncrasy (propiverine hydrochloride) or hypersensitivity (excipients)

- **Renal and urinary disorders**
Uncommon: urinary retention

**General disorders and administration site conditions**
Common: fatigue

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: G04BD06
Pharmacotherapeutic group: urinary antispasmodics

**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 pelvis 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**

**Absorption**
After oral administration of Mictonorm XL 45 mg Capsules propiverine is absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 9 to 10 hours. The mean absolute bioavailability of Mictonorm XL 45 mg Capsules is 59.5 ± 23.3% (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.

**Distribution**
After administration of Mictonorm XL 45 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, ± SD, range) of propiverine in 10 healthy volunteers after single dose administration of Mictonorm XL 30 mg Modified Release Capsules and Mictonorm XL 45 mg Modified Release Capsules:**

<table>
<thead>
<tr>
<th>Dose [mg]</th>
<th>30</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-∞ [ng h/ml]</td>
<td>1378 (903, 2104)</td>
<td>1909 (1002, 3639)</td>
</tr>
<tr>
<td>C_{max} [ng/ml]</td>
<td>60.6 (41.5, 88.6)</td>
<td>80.0 (41.8, 152.1)</td>
</tr>
<tr>
<td>t_{1/2} [h]</td>
<td>14.2 (10.8, 18.6)</td>
<td>16.3 (13.9, 19.2)</td>
</tr>
<tr>
<td>t_{max} [h]</td>
<td>9.9 ± 2.4</td>
<td>9.9 ± 2.4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>geometric mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC 0-24h [ng h/ml]</td>
</tr>
<tr>
<td>PTF [%]</td>
</tr>
<tr>
<td>C_{av} [ng/ml]</td>
</tr>
<tr>
<td>C_{max} [ng/ml]</td>
</tr>
<tr>
<td>C_{min} [ng/ml]</td>
</tr>
<tr>
<td>t_{1/2} [h]</td>
</tr>
<tr>
<td>t_{max} [h]</td>
</tr>
</tbody>
</table>

PTF: peak-trough fluctuation

**Biotransformation**

Propiverine is extensively metabolised by intestinal and hepatic enzymes. The primary metabolic route involves the oxidation of the Piperidyl-N and is mediated 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
Following oral administration of 10 – 45 mg of propiverine hydrochloride the C\text{max} and the AUC\text{0-∞} increased dose-proportionally.

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. However, in patients with severe renal impairment (creatinine clearance < 30 ml/min) the maximum daily dose of propiverine is 30 mg. Mictonorm XL 45mg Modified-Release Capsules is not recommended in patients with severe renal failure.

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.

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. 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.

No effects on male and female fertility and reproduction behaviour were observed in toxicological studies with rats.

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**
3 years
Bottle:
Stability after first opening: 100 days

6.4 **Special precautions for storage**
Blister:
Store in the original package to protect from moisture.
Do not store above 25 °C.

Bottle:
Keep the bottle tightly closed.

6.5 **Nature and contents of container**
Blisters of PVC/TE/PVDC and aluminium foil in cartons of 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112, 168 or 280 capsules.
Polyethylene bottles with a polypropylene screw cap containing a silica gel desiccant of 10, 14, 20, 28, 30, 49, 50, 56, 60, 84, 98 or 100 capsules.
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
not applicable

7 **MARKETING AUTHORISATION HOLDER**
APOGEPHA Arzneimittel GmbH
Kyffhäuserstraße 27
01309 Dresden
Germany

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 15072/0010

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
30/11/2009

10 **DATE OF REVISION OF THE TEXT**
18/07/2011
Module 3
Patient Information Leaflet
The MAH has submitted a test version only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before the packs are marketed.

PACKAGE LEAFLET: INFORMATION FOR THE USER

MICTONORM® XL 45 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, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The name of your medicine is Mictonorm XL 45 mg Modified Release Capsules (referred to as Mictonorm XL 45 mg throughout this leaflet). The active substance is propiverine hydrochloride and the other ingredients are listed at the end of the leaflet (Section 6, Further Information).

In this leaflet:
1. What Mictonorm XL 45 mg is and what it is used for
2. Before you take Mictonorm XL 45 mg
3. How to take Mictonorm XL 45 mg
4. Possible side effects
5. How to store Mictonorm XL 45 mg
6. Further information

1. What Mictonorm XL 45 mg is and what it is used for

Mictonorm XL 45 mg is used for the treatment of people who have difficulty in controlling their bladders due to bladder overactivity or who have problems with the spinal cord. Mictonorm XL 45 mg contains the active substance propiverine hydrochloride. This substance prevents the bladder from contracting and increases the amount that the bladder can hold. Mictonorm XL 45 mg is used to treat the symptoms of overactive bladder. It is a modified-release capsule that needs to be taken once a day.

2. Before you take Mictonorm XL 45 mg

Do not take Mictonorm XL 45 mg

Do not take Mictonorm XL 45 mg if you are allergic (hypersensitive) to propiverine hydrochloride or to any of the other ingredients of Mictonorm XL 45 mg (these are listed in section 6, Further information).

Do not take Mictonorm XL 45 mg if you suffer from any of the following conditions:
- obstruction of the bowel
- obstruction to the bladder outlet (difficulty in passing urine)
- myasthenia gravis (a disease causing muscle weakness)
- a loss of function of the muscles controlling your bowel movements (intestinal atony)
- severe inflammation of the bowel (ulcerative colitis) that may lead to diarrhoea containing blood and mucus and stomach pain
- toxic megacolon (a condition involving enlargement of the bowel)
- increased pressure in the eye (uncontrolled angle closure glaucoma)
- moderate or severe liver disease
- fast and irregular heart beat

**Take special care with Mictonorm XL 45 mg**

Before you take Mictonorm XL 45 mg you should tell your doctor if you have:

- damage to the nerves that control blood pressure, heart rate, bowel and bladder movements and other bodily functions (autonomic neuropathy)
- severe kidney problems
- moderate or severe liver problems
- severe heart failure
- enlargement of the prostate gland
- heartburn and indigestion due to back flow of gastric juice into the throat (hiatus hernia with reflux oesophagitis)
- irregular heart beat
- fast heart beat

If you suffer from any of these conditions, contact your doctor. He will tell you what to do.

**Taking other medicines**

You should tell your doctor if you are taking or have taken any of the following medicines as they may interact with Mictonorm XL 45 mg:

- antidepressants (e.g. imipramine, clomipramine and amitriptyline).
- sleeping tablets (e.g. benzodiazepines),
- anticholinergics taken by mouth or injection (usually used to treat asthma, stomach cramps, eye problems or urinary incontinence),
- amantadine (used to treat flu and Parkinson’s disease)
- neuroleptics such as promazine, olanzapine, quetiapine (drugs used to treat psychotic disorders like schizophrenia or anxiety),
- beta stimulants (drugs used to treat asthma),
- isoniazid (a treatment for tuberculosis) and
- metoclopramide (used to treat nausea and vomiting)

Nevertheless, it may still be all right for you to take Mictonorm XL 45 mg. Your doctor will be able to decide what is suitable for you.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Taking Mictonorm XL 45 mg with food and drink

The capsules should be swallowed with or without food or drink.

Pregnancy and breast-feeding

Do not take Mictonorm XL 45 mg if you are pregnant, likely to become pregnant or are breast-feeding.

Driving and using machines

Mictonorm XL 45 mg can sometimes cause sleepiness and blurred vision. You should not drive or operate machinery if you suffer from sleepiness and blurred vision.

Important information about some of the ingredients of Mictonorm XL 45 mg

Mictonorm XL 45 mg contains lactose (a sugar). If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Mictonorm XL 45 mg

Always take Mictonorm XL 45 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The label on the carton will tell you how many capsules you should take and when. Take your capsule at the same time each day. Swallow it with or without food or drink. Do not crush or chew the capsules.

Adults and the elderly: The usual dose of Mictonorm XL 45 mg is one capsule daily.

Mictonorm XL 45 mg is not recommended for children.

If you take more Mictonorm XL 45 mg than you should

If you have accidentally taken more than your prescribed dose, contact your nearest casualty department or tell your doctor or pharmacist immediately. Remember to take the pack and any remaining capsules with you.

If you forget to take Mictonorm XL 45 mg

Do not worry. Simply leave out that dose completely. Then take your next dose at the right time. Do not take a double dose to make up for a missed dose.

4. Possible side effects

Like all medicines, Mictonorm XL 45 mg can cause side effects, although not everybody gets them. All medicines can cause allergic reactions although serious allergic reactions are very rare. The following symptoms are first signs for such reactions:

- Any sudden wheeziness, difficulty in breathing or dizziness, swelling of the eyelids, face, lips or throat
- Peeling and blistering of the skin, mouth, eyes and genitals
- Rash affecting your whole body.
If you get any of these symptoms during treatment, you should stop taking the capsules and contact your doctor immediately.

You might suffer an acute attack of glaucoma. In this case, you have been seeing coloured rings around lights or develop severe pain in and around either eye. You should seek medical attention immediately.

The following side effects have also been reported:

**Very common** (affects more than 1 user in 10)
- dry mouth

**Common** (affects 1 to 10 users in 100)
- abnormal vision and difficulty in focusing
- fatigue
- headache
- stomach pain
- indigestion
- constipation

**Uncommon** (affects 1 to 10 users in 1,000)
- feeling sick and vomiting
- dizziness
- trembling (tremor)
- difficulty in passing urine (urinary retention)
- flushing
- altered sense of taste
- decreased blood pressure with drowsiness

**Rare** (affects 1 to 10 users in 10,000)
- rash

**Very rare** (affects less than 1 user in 10,000)
- irregular heartbeat
- restlessness and confusion

**Not known** (frequency cannot be estimated from the available data)
- sensing things that are not real (hallucination)

If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Mictonorm XL 45 mg

Keep out of the reach and sight of children.

Do not use Mictonorm XL 45 mg after the expiry date, which is stated on the blister or bottle and carton after EXP. The expiry date refers to the last day of that month.

- **Blister:** Do not store above 25°C. Store in the original package to protect the capsules from moisture.
- **Bottle:** Keep the bottle tightly closed.
  Stability after first opening of the bottle: 100 days.
6. Further information

What Mictonorm XL 45 mg contains

The active substance is propiverine hydrochloride. Each capsule contains 45 mg of modified release propiverine hydrochloride

The other ingredients are 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, gelatine, titanium dioxide E171, red iron oxide E172, and yellow iron oxide E172.

What Mictonorm XL 45 mg looks like and contents of the pack

Mictonorm XL 45 mg capsules are orange containing white to off-white pellets.

They are available in
- cartons of 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112, 168 or 280 capsules.
- bottles of 10, 14, 20, 28, 30, 49, 50, 56, 60, 84, 98 or 100 capsules.

The polyethylene bottles with a polypropylene screw cap contain a silica gel desiccant.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

APOGEPHA Arzneimittel GmbH
Kyllhäuserstraße 27
01309 Dresden
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

- Germany: Mictonorm Uno® 45 mg Harpkapseln mit veränderter Wirkstofffreisetzung
- United Kingdom: Mictonorm® XL 45 mg Modified-Release Capsules
- Ireland: Dervonorm® XL 45 mg Modified-Release Capsules
- Austria: Mictonorm® 45 mg Harpkapseln mit veränderter Wirkstofffreisetzung
- Belgium: Mictonorm® Forte 45 mg Capsule met geregelde afgifte
- Czech Republic: Mictonorm Uno® 45 mg Tvrđe tobolky s řízeným uvoľňováním
- Greece: Mictonorm® Uno 45 mg Κάψουλες ελεγχόμενης αποδόσεως
- Italy: Mictonorm® 45 mg Capsule a rilascio modificato
- Luxembourg: Mictonorm® Forte 45 mg Géhules à libération modifiée
- Slovak Republic: Mictonorm® XL 45 mg Tvrda kapsula s riadeným uvoľňovaním
- Slovenia: Mictonorm® 45 mg Trde kapsule s prirejenim sprotčanjem
- Portugal: Mictonorm® OD 45 mg Cápsula de libertação modificada

This leaflet was last approved in 07/2011.
Module 4
Labelling

The MAH has submitted text versions only and has committed to submitting mock-up delivery to the relevant regulatory authorities for approval before packs are marketed.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

Mictonorm XL 45 mg Modified release capsules
Propiverine Hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified release capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 modified release capsules
14 modified release capsules
20 modified release capsules
28 modified release capsules
30 modified release capsules
49 modified release capsules
50 modified release capsules
56 modified release capsules
60 modified release capsules
84 modified release capsules
98 modified release capsules
100 modified release capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. **EXPIRY DATE**

Expiry date:
Stability after first opening: 100 days

9. **SPECIAL STORAGE CONDITIONS**

Keep the bottle tightly closed.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

APOGEPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01309 Dresden, Germany

12. **MARKETING AUTHORISATION NUMBER (S)**

PL 15072/0010

13. **BATCH NUMBER**

Batch number:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

Do not crush or chew.

16. **INFORMATION IN BRAILLE**

MICTONORM XL 45 MG
MINIMUM PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLES

1. NAME OF THE MEDICINAL PRODUCT
Mictonorm XL 45 mg Modified release capsules
Propiverine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each modified release capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).

3. LIST OF EXCIPIENTS
Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS
10 modified release capsules
14 modified release capsules
20 modified release capsules
28 modified release capsules
30 modified release capsules
49 modified release capsules
50 modified release capsules
56 modified release capsules
60 modified release capsules
84 modified release capsules
98 modified release capsules
100 modified release capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.
7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
Expiry date:
Stability after first opening: 100 days

9. SPECIAL STORAGE CONDITIONS
Keep the bottle tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER
APOGEPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01309 Dresden, Germany

12. MARKETING AUTHORISATION NUMBER(S)
PL 15072/0010

13. BATCH NUMBER
Batch number:

14. GENERAL CLASSIFICATION FOR SUPPLY
Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE
Do not crush or chew.

16. INFORMATION IN BRAILLE
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BlistERS

17. NAME OF THE MEDICINAL PRODUCT

Mictonorm XL 45 mg Modified release capsules
Propiverine hydrochloride

18. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified release capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).

19. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

20. PHARMACEUTICAL FORM AND CONTENTS

14 modified release capsules
20 modified release capsules
28 modified release capsules
30 modified release capsules
49 modified release capsules
50 modified release capsules
56 modified release capsules
60 modified release capsules
84 modified release capsules
98 modified release capsules
100 modified release capsules
112 modified release capsules
168 modified release capsules
280 modified release capsules

21. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

22. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.
23. OTHER SPECIAL WARNING(S), IF NECESSARY

24. EXPIRY DATE

Expiry date:

25. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package to protect from moisture.

26. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

27. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

APOGEPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01369 Dresden, Germany

28. MARKETING AUTHISATION NUMBER(S)

PL 15072/0010

29. BATCH NUMBER

Batch number:

30. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

31. INSTRUCTIONS ON USE

Do not crush or chew.

32. INFORMATION IN BRAILLE

MICTONORM XL 45 MG
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALUMINIUM/PVC BLISTERS</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**
   - Mictonorm XL 45 mg Modified Release Capsules
   - Propiverine hydrochloride

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**
   - APOGEPHA Arzneimittel GmbH

3. **EXPIRY DATE**
   - Expiry date:

4. **BATCH NUMBER**
   - Batch number:

5. **OTHER**
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Mictonorm XL 45 mg Modified-Release Capsules, used for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder syndrome or neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord injuries, is approvable. A national Marketing Authorisation was granted on 30th November, 2009.

EXECUTIVE SUMMARY
Problem statement
This mutual recognition application, submitted under Article 8.3 (known active substance) of Directive 2001/83/EC (as amended), considers Mictonorm XL 45 mg Modified-Release Capsules (PL 15072/0010, UK/H/4594/01/MR). This medicinal product was granted a national Marketing Authorisation in the UK in November 2009, as a line extension, with respect of an additional dosage, to Mictonorm XL 30mg Modified-Release Capsules (PL 15072/0006, MRP UK/H/0917/01), which was itself considered a line extension, with respect of an additional dosage and a new pharmaceutical form, to Mictonorm 15mg coated tablets (PL 15072/0002, MRP UK/H/0271/01). The indications of Mictonorm XL 45 mg Modified-Release Capsules (PL 15072/0010, UK/H/4594/01/MR) are identical to those of Mictonorm 15mg coated tablets (PL 15072/0002, MRP UK/H/0271/01).

With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, APOGEPHA Arzneimittel GmbH, is applying for a Marketing Authorisation for Mictonorm XL 45 mg Modified-Release Capsules in Austria, Belgium, Czech Republic, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Slovenia and Slovakia (UK/H/4594/001/MR).

Clinical pharmacokinetics and pharmacodynamics of propiverine are well-known, reference is made to PL 15072/0002 (MRP UK/H/0271/01) and PL 15072/0006 (MRP UK/H/0917/01). The application is supported by a series of pharmacokinetic and clinical efficacy studies, as detailed in the Clinical Aspects of this report.

The approved SmPC is satisfactory from the clinical and pharmaceutical point of view, and consistent with the SmPCs for Mictonorm 15mg coated tablets (PL 15072/0002, MRP UK/H/0271/01) and Mictonorm XL 30mg Modified-Release Capsules (PL 15072/0006, MRP UK/H/0917/01). The currently approved full SmPC is provided in Module 2 of this report.

The approved PIL is an accurate reflection of the SmPC and complies with the appropriate guidelines. The leaflet has been prepared in accordance with Articles 59(3) and 63(1) of Council Directive 2001/83/EC, as amended. User testing of the package leaflet has been evaluated and accepted. The current UK-approved PIL is provided in Module 3 of this report.
About the product
This medicinal product contains propiverine hydrochloride as the active ingredient. Propiverine hydrochloride belongs to the pharmacotherapeutic group: urinary antispasmodics (ATC code G04B D06) and is well characterised in the literature.

The posology is consistent with the dosing instructions for the immediate release tablets (15mg) and modified release capsules (30mg). The development of this product was based on the rationale that there is a relationship between the pharmacological/toxicological response and the systemic exposure to the drug/metabolites. The aim of the development was to reach a similar total exposure to the drug as for the immediate-release (IR) formulation.

General comments on the submitted dossier
The active substance is not a new active substance. Propiverine hydrochloride is an established product with a well characterised safety profile.

The application is in accordance with Article 8.3 (known active substance) of Directive 2001/83EC, as amended. The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall quality and clinical overviews have been submitted. They represent an adequate summary of the dossiers.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
This application has been submitted under Article 8.3 (known active substance) of Directive 2001/83/EC (as amended). The application cross-references the pre-clinical data submitted for Mictonorm 15mg coated tablets (PL 15072/0002, MRP UK/H/0271/01), which has been through 2 successful MRPs. The application is supported by a series of pharmacokinetic and clinical efficacy studies, as detailed in Module 5 of the Assessment Report.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

No issues regarding GLP or GCP aspects have been identified during the review of the dossier.
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

**DRUG SUBSTANCE**  
Propiverine hydrochloride

rINN name: Propiverine hydrochloride  
Chemical name: 2,2-diphenyl-2-(1-proproxy)aceticacid-(1-methylpiperid-4-yl)ester hydrochloride  
Molecular formula: C\textsubscript{23}H\textsubscript{30}ClNO\textsubscript{3}  
Molecular weight: 403.95

**Structure**

![Propiverine Hydrochloride Structure](image)

**General properties**

**General Properties**  
Propiverine hydrochloride is a white to almost white powder that is freely soluble in water and freely soluble in methanol, soluble in anhydrous ethanol and practically insoluble in acetone.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

A GMP certificate is provided for the active ingredient manufacturer.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Acceptable certificates of analysis have been provided for each intermediate.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.
Propiverine hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Stability data have been provided in accordance with regulatory requirements and support the declared retest interval.

**DRUG PRODUCT**

**Description and Composition**

The proposed product is presented as a modified release hard capsule, orange in colour containing white to off-white pellets. Each capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).

Other ingredients consist of pharmaceutical excipients, namely citric acid, povidone, lactose monohydrate, talc, triethyl citrate, magnesium stearate, methacrylic acid–methyl methacrylate copolymer (1:1) [Eudragit L®], methacrylic acid-methyl methacrylate copolymer (1:2) [Eudragit S®], ammonio methacrylate copolymer type A [Eudragit RL®] and ammonio methacrylate copolymer type B [Eudragit RS®] making up the pellets and gelatin, Titanium dioxide E171, red iron oxide E172 and yellow iron oxide E172 making up the capsule.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory specifications and certificates of analysis have been provided for all excipients. A suitable justification for the use of each excipient has been provided and is satisfactory.

With the exception of the lactose monohydrate, Eudragit products, gelatin and magnesium stearate none of the other excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption. Satisfactory Certificates of Suitability issued by the European Directorate for the Quality of Medicines (EDQM), confirming that the gelatine, magnesium stearate and Eudragit products have been manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Comparative dissolution profiles for the test product, Mictonorm XL 45 mg Modified Release Capsules and the comparator product, Mictonorm 15mg coated tablets (PL 15072/0002), were provided and were found to be comparable.

**Manufacturer(s)**

A narrative description and flow-chart of the manufacturing method has been provided.
In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. The process validation data demonstrated consistency of the manufacturing process.

**Finished product specification**

Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure system**

The packaging consists of either polyethylene (PE) bottles with a polypropylene (PP) screw cap containing a silica gel desiccant or blisters composed of polyvinylchloride (PVC), thermo elastomer (TE) and polyvinylidene chloride (PVDC) and aluminium foil. The blister strips contain 7, 10 or 14 capsules and are packaged with the PIL into cardboard outer cartons in numerous pack sizes - 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112, 168, 168 (2 x 84) or 280 (28 x 10) capsules. The PE bottles, with PP screw caps, are in numerous pack sizes- 10, 14, 20, 28, 30, 49, 50, 56, 60, 84, 98 or 100 capsules. The MAH stated that not all the pack sizes may be marketed and commits to submit mock-ups for packs sizes prior to marketing.

Specifications and certificates of analysis for all packaging components used have been provided. This is satisfactory. All the primary product packaging that is in direct contact with the drug product complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf life of 3 years have been set with storage conditions of ‘Do not store above 25 degree C’ and ‘Store in the original package to protect from moisture’ for the blister and ‘Keep the bottle tightly closed’ for the bottle container have been approved.

**Bioequivalence/bioavailability**

The application is supported by a series of pharmacokinetic and clinical efficacy studies, as detailed in Clinical Aspects of this Assessment Report. The studies were of an appropriate design and were conducted to the principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and originator products.

**Expert Report**

A satisfactory quality overall summary is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The approved SmPC, Patient Information Leaflet and labelling texts are satisfactory. The MAH has submitted text versions of the PIL and labelling only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The user testing of the PIL text has been evaluated and is accepted. The labelling texts fulfil the statutory requirements for Braille.

MAA Forms
The MAA form is pharmaceutically satisfactory.

Conclusion
There are no objections to the approval of Mictonorm XL 45 mg Modified Release Capsules.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of propiverine hydrochloride are well-known. There are no novel excipients. No new non-clinical studies were conducted, which is acceptable given that the application is based on a well-known active substance that has been used in other licences granted previously. No new non-clinical data were supplied with this application and none are required since this application is submitted as an extension of a complete application, cross-reference is made to the pre-clinical data submitted for Mictonorm 15mg coated tablets (PL 15072/0002, MRP UK/H/0271/01). This is acceptable.

ENVIRONMENTAL RISK ASSESSMENT (ERA)
As part of the screening for persistence, bioaccumulation and toxicity, the applicant has provided log $K_{ow}$ values of 1.11, 2.36, 4.01 and 4.72 at pH 5.0, 6.0, 7.0 and 8.0, respectively. However, it is noted that the method used to determine log $K_{ow}$ was not provided.

Using the default values in the guideline, the PEC_{SURFACE\WATER} was calculated as follows:

$$\text{PEC}_{sw} = \frac{45 \times 0.01}{200 \times 10} = 0.000225 \text{ mg/L} = 0.225 \mu\text{g/L}$$

The calculated PEC_{SURFACE\WATER} value (based upon a maximum dose of 45 mg per day) was above the threshold of 0.01 $\mu$g/L; hence, a Phase II environmental risk assessment was conducted.

The applicant has performed studies to assess the toxicity of propiverine hydrochloride on algae, Daphnia sp., fish and microbial communities. Brief summary reports have been provided. In addition, studies were conducted to determine whether the drug substance is readily biodegradable.
Following repeated-administration, the no effect concentrations for algae and Daphnia species were 0.32 mg/L, and 0.98 mg/L, respectively. Based upon the lowest no effect concentration (0.32 mg/L) and upon application of the assessment factor (AF), the PNEC_{WATER} was estimated to be 0.032 mg/L.

\[
\text{PEC}_{SW}:\text{PNEC}_{WATER} = \frac{0.000225 \text{ mg/L}}{0.032 \text{ mg/L}} = 0.00703
\]

The PEC_{SW}:PNEC_{WATER} ratio is below 1; hence, the applicant has concluded that the drug substance is unlikely to represent a risk to the aquatic environment and that further testing in the aquatic environment is not necessary. However, it is noted that an acute/short-term study was performed to evaluate the effects on fish.

The PEC_{GROUNDWATER}:PNEC_{GROUNDWATER} ratio was also calculated:

\[
\text{PEC}_{GROUNDWATER} = 0.25 \times \text{PEC}_{SURFACE \ \text{WATER}} = 0.25 \times 0.000225 \text{ mg/L} = 0.00005625 \text{ mg/L}
\]

In accordance with the regulatory guideline for environmental risk assessments, the PNEC_{GROUNDWATER} is based upon the no effect concentration for the Daphnia species, which is 0.98 mg/L.

Hence, \[
\text{PEC}_{GROUNDWATER}:\text{PNEC}_{GROUNDWATER} = \frac{0.00005625 \text{ mg/L}}{0.098 \text{ mg/L}} = 5.739 \times 10^{-4}
\]

The PEC_{GW}:PNEC_{GW} ratio is below 1; hence, the applicant has concluded that further testing in the aquatic environment is not necessary.

It is noted that the environmental risk assessment was performed in accordance with the CPMP discussion paper on Environmental Risk Assessment of non-genetically modified organism (non GMO) containing medicinal products for human use (dated 25th January 2001). However the environmental risk assessment provided was signed off in February 2007, when the final EMEA guideline [EMEA/CHMP/SWP/4447/00] was in effect. Hence, for the completion of the environmental risk assessment of propiverine hydrochloride, the applicant should submit the following studies:

- Adsorption – Desorption study using a batch equilibrium method (determination of K_{oc})
- Chronic studies that evaluate the effects on fish. Acute studies are not reflective of the clinical situation, where low sub-lethal levels of drug are present constantly or over a prolonged period. The data derived from the acute toxicity study may aid dose selection for the repeated-dose studies.
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD308), as the applicant has indicated that biodegradation was low and/or that the results of this study were inconclusive.

In addition, the applicant should clarify the methods used to determine log K_{OW} and comment on the relevance of the log K_{OW} value (at pH 8) above the threshold of 4.5.
Overall Summary and Conclusion

The Marketing Authorisation Holder (MAH) has provided an Environmental Risk Assessment (dated February, 2007); however, the data provided are considered insufficient and not in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use which came into effect in 2006 [EMEA/CHMP/SWP/4447/00]. Hence, the MAH should also conduct the following (i) an adsorption – desorption study, (ii) an early life stage toxicity test in fish (chronic) (iii) studies to investigate the effects of propiverine on aerobic and anaerobic transformation in aquatic systems. The applicant will submit the results of these studies for assessment.

NON-CLINICAL OVERVIEW
The non-clinical overall summary was written by a suitably qualified person and is satisfactory. The curriculum vitae of the expert has been provided.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)
The SmPC is satisfactory from a non-clinical viewpoint and is consistent with that for the originator product.

In conclusion, the non-clinical aspects can be considered to be resolved, except for the issue of the ERA, which may be resolved as a post MRP authorisation commitment. There are no objections to the approval of Mictonorm XL 45 mg Modified Release Capsules from a non-clinical point of view.

III.3 CLINICAL ASPECTS

3.1 BACKGROUND
Mictonorm/Propinorm XL 45mg are modified-release capsules containing propiverine hydrochloride as active substance which calcium-modulating and anticholinergic properties. The drug was developed as a modified release formulation with the intention to increase patient’s compliance (once daily formulation) and to lower the incidence of adverse drug effects.

Active ingredient propiverine belongs to the pharmacotherapeutic group of spasmolytic, anticholinergic agents and has an ATC Code of G04B D06.

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

The indications are consistent with those for the originator products and are satisfactory.

3.3 Dose & Dose Schedule
The recommended daily dose is one capsule (= 45 mg propiverine hydrochloride) once a day.
The posology is consistent with the dosing instructions for the currently approved immediate release tablets and modified release capsules.

3.4 Clinical Pharmacology

3.4.1 Pharmacodynamics

No new data were submitted.

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04B D06

Propiverine hydrochloride, referred to in the following as propiverine (P4), is a detrusor relaxant drug. Drugs with a comparable pharmacodynamic profile are tolterodine and oxybutynin. Clinical pharmacokinetics and pharmacodynamics of propiverine are well-known, reference is made to PL 15072/0002 (MRP UK/H/0271/01) and PL 15072/0006 (MRP UK/H/0917/01).

Propiverine inhibits calcium influx and modulates intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis. It also inhibits the efferent connection of the nervus pelvis due to anticholinergic action.

In animal models propiverine 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.

3.4.2 Pharmacokinetics

The following studies were performed to assess bioavailability and to support marketing approval of the new 45 mg ER formulation.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study design</th>
<th>Area of investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P 387</td>
<td>open, prospective, cross-over</td>
<td>site of intestinal absorption</td>
</tr>
<tr>
<td>P 426</td>
<td>randomized, prospective, cross-over</td>
<td>comparative BA</td>
</tr>
<tr>
<td>P 506.1</td>
<td>double blind, randomized, cross-over</td>
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<td>P 702</td>
<td>open, randomized, cross-over</td>
<td>in vitro-in vivo correlation</td>
</tr>
<tr>
<td>P 701</td>
<td>double blind, randomized, cross-over</td>
<td>dose proportionality, absolute BA</td>
</tr>
<tr>
<td>P 703</td>
<td>open, randomized, cross-over</td>
<td>food-drug interaction</td>
</tr>
</tbody>
</table>

3.4.2.1 Supportive PK studies

P 387: The absorption of propiverine hydrochloride (P4) from different sites of the small intestine was examined in an open, prospective, cross-over study.
Dissolved propiverine (15 mg) was given to 4 male healthy subjects via intestinal tubing into different parts of the small intestine (a proximal and a considerably more distal site). The bioavailability of P4 was not different between the lower part of the small intestine compared to the upper small bowel. There was a greater AUC of metabolite P4NO after proximal intestinal administration compared to the more distal one. Taken together, the results of this study provide a rational basis for the development of an extended-release formulation of P4.

**P 426:** Basic pharmacokinetic parameters of P4 and its main metabolite P4NO after oral administration of newly developed extended-release formulations were assessed in a randomized, open, 3-period, cross-over, mono-centric study. Propiverine was administered as a single oral dose to 6 healthy male volunteers at the following dosages:

- formulation P1 (22.5 mg) immediate-release (batch G224X026/22.5)
- formulation P2 (45 mg) extended-release (batch G224X044a)
- formulation P3 (45 mg) extended-release (batch G224X038)

The three pellet formulations differed in their *in vitro* dissolution rate.

A comparison between the three formulations, using dose corrected values for formulation P1, is given in the table below.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation</th>
<th>P4 Point estimate (95% CI)</th>
<th>P4NO Point estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{P4}</td>
<td>P2/P1</td>
<td>1.06 (0.70 - 1.42)</td>
<td>0.68 (0.52 - 0.60)</td>
</tr>
<tr>
<td></td>
<td>P3/P1</td>
<td>1.05 (0.72 - 1.53)</td>
<td>0.61 (0.47 - 0.78)</td>
</tr>
<tr>
<td>AUC_{P4}</td>
<td>P2/P1</td>
<td>1.15 (0.73 - 1.80)</td>
<td>0.77 (0.55 - 1.07)</td>
</tr>
<tr>
<td></td>
<td>P3/P1</td>
<td>1.39 (0.79 - 2.42)</td>
<td>0.76 (0.50 - 0.66)</td>
</tr>
<tr>
<td>C_{max}</td>
<td>P2/P1</td>
<td>0.49 (0.37 - 0.65)</td>
<td>0.30 (0.25 - 0.40)</td>
</tr>
<tr>
<td></td>
<td>P3/P1</td>
<td>0.37 (0.27 - 0.51)</td>
<td>0.19 (0.17 - 0.22)</td>
</tr>
</tbody>
</table>

Compared to the immediate-release formulation P1 (considered as reference after dose correction), the extended-release formulations P2 and P3 revealed no differences in the bioavailability of the parent drug. The amount of P4NO was significantly reduced after administration of P2 and P3 compared to P1. In agreement with the extended-release characteristics of P2 and P3, the rate of absorption of propiverine was significantly reduced with lower C_{max} values compared to the results of formulation P1.

**3.4.2.2 Pivotal PK studies**

**P 506,1:** A multiple dose bioequivalence study was performed to compare the marketed immediate release formulation with an extended-release formulation of propiverine chosen for further development. The study design was randomized, double blind, double dummy, multiple dose, two period cross-over. Treatment was given for 7 days, there was a washout period of 14 days between treatments.
28 healthy volunteers (14 male, 14 female) aged 20 to 29 years were enrolled into the study. 4 subjects discontinued prematurely, 24 subjects completed the study and were included in PK analysis. Subjects received either 45 mg extended-release propiverine multiunit capsules once daily (Test, batch number G224X085) or 15 mg immediate-release tablets t.i.d. (Reference, batch number 708042) for 7 days.

Blood samples were taken before drug administration on treatment days 2 - 7 (trough values) and on treatment day 7 up to 72 hours after drug administration. On the treatment days 1 to 6, the study medication was given after a meal. The last meal in the evening of the 6th treatment day had to be before 9 p.m. On the day of dense PK sampling, study drug was administered at 7 am, light breakfast was served at 11 am and dinner at 7 pm.

Propiverine (P4) and its major N-oxidised metabolite P4NO in serum and urine were assayed quantitatively using an HPLC-method after solid-phase extraction (Richter et al. 1998). The assay was validated for 10-1000 ng/ml propiverine and 20-1000 ng/ml propiverine N-oxide.

Recovery for P4 and P4NO was found to be 99% and 95%, respectively. Linear regression with the weighing factor 1/x was used to calculate concentrations in unknown samples. Study samples were analysed in 48 analytical runs. Within study accuracy and precision was proven based on the back-calculated concentrations of calibration curve samples and quality control samples in duplicates.

PK analysis and BE calculation were performed using the ANOVA test and the EquivTest v.1.0. software.

<table>
<thead>
<tr>
<th></th>
<th>Test Mean ± SD</th>
<th>Reference Mean ± SD</th>
<th>Test-Reference point estimate (90 % confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[h]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propiverine</td>
<td>7.44 ± 2.24</td>
<td>4.46 ± 3.86</td>
<td>2.979 (1.624, 4.334)</td>
</tr>
<tr>
<td>Propiverine N-oxide</td>
<td>7.94 ± 2.74</td>
<td>3.56 ± 3.37</td>
<td>4.875 (2.500, 6.500)</td>
</tr>
</tbody>
</table>

Bioequivalence range: Value of Reference ± 20 %
Steady state was achieved after the 7 days of treatment based on the trough concentrations. The trough concentrations of the extended-release formulation (Test, given once daily) was equivalent to the Reference formulation given t.i.d. with regard to the extent of absorption as determined by the AUC0-24h. Test was also equivalent to Reference with regard to the average steady-state serum concentrations (Cav) reached on the 7th treatment day (71 vs 70 ng/ml). The mean values for Cmax, Cmin and PTF of the parent compound were slightly lower for the Test compared to the Reference with point estimates within the standard 90% confidence interval.

**Figure 1.** Trough serum concentrations (geometric means) of propiverine in the mornings of the treatment days 4-7 and concentration-time profiles on the 7th treatment day (0-24 h) after administration of Test and Reference in 24 volunteers.
The results of the selected pharmacodynamic assessments (mean±SD) before, during the treatment with propiverine and thereafter up to day 10 are shown in the Figures below. All characteristics changed in the same manner after Test and Reference treatment.

Table D5: Geometric means, sd-factor (sd-range) of concentrations of propiverine HCl and propiverine N-oxide after administration of 3 x 15 mg Mictonorm and 45 mg Propiverine UNO, resp. (grey lines are trough levels)

<table>
<thead>
<tr>
<th>time [h]</th>
<th>propiverine conc. [ng/ml]</th>
<th>propiverine N-oxide conc. [ng/ml]</th>
<th>propiverine conc. [ng/ml]</th>
<th>propiverine N-oxide conc. [ng/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5 d</td>
<td>0.0, 0.0 (0.0, 0.0)</td>
<td>0.0, 0.0 (0.0, 0.0)</td>
<td>0.0, 0.0 (0.0, 0.0)</td>
<td>0.0, 0.0 (0.0, 0.0)</td>
</tr>
<tr>
<td>-3 d</td>
<td>57.0, 1.53 (37.8, 86.6)</td>
<td>34.8, 1.60 (216, 556)</td>
<td>58.8, 1.51 (36.1, 84.8)</td>
<td>244.0, 1.64 (146, 354)</td>
</tr>
<tr>
<td>-2 d</td>
<td>53.9, 1.58 (35.9, 83.3)</td>
<td>27.1, 1.49 (249, 552)</td>
<td>59.7, 1.58 (37.0, 94.4)</td>
<td>239.1, 1.50 (152, 363)</td>
</tr>
<tr>
<td>-1 d</td>
<td>54.2, 1.60 (42.7, 96.4)</td>
<td>35.8, 1.62 (235, 545)</td>
<td>57.8, 1.71 (33.3, 86.3)</td>
<td>245.1, 1.50 (150, 378)</td>
</tr>
<tr>
<td>0</td>
<td>54.4, 1.60 (42.8, 96.8)</td>
<td>37.2, 1.57 (237, 582)</td>
<td>59.5, 1.60 (37.1, 96.5)</td>
<td>255.1, 1.52 (162, 388)</td>
</tr>
</tbody>
</table>

Figure 2: Salivation (mean ± SD) after chewing a piece (5 x 5 cm) of PARAFILM M® for 5 min in 24 healthy subjects before (baseline, day 1), at treatment days 4-7 and 3 days thereafter (9-10)
Safety measurements revealed the spectrum of typical expected adverse drug reactions with anticholinergic properties such as dry mouth, disturbances of vision and obstipation. Other adverse events were either not of clinical relevance or were judged not to be related to the study medication.

The rate of absorption from the IR and ER formulations was different as expected. \( T_{\text{max}} \) for ER formulation was 7.3 h and for the IR formulation 4.7 h. \( T_{1/2} \) for the ER product was 20 h and for the IR 14 h. However, the AUC, Cmax, Cmin and fluctuation were within the standard BE criteria. The systemic exposure at steady state between the IR and ER formulations was similar.

The BE was shown for the parent compound propiverine.

Based on the study results it can be concluded that the 15 mg t.i.d IR tablet is interchangeable with the 45 mg ER capsule.

BE criteria for the metabolite P4NO were slightly outside from the standard range. However, since P4NO is much less pharmacologically active than the parent compound, the decision on BE should be primarily based on the parent compound data.

The following has been approved for the 30mg XL propiverine capsules (source SmPC):

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.

\textbf{P 702}: This study was carried out with the attempt to establish a point-to-point \textit{in vitro-in vivo} correlation (IVIVC) according to the Note for Guidance on Quality of Modified Release Products: A. Oral dosage forms B: Transdermal dosage forms, section I (quality), CPMP/QWP/604/96.
Based on the results of a first pilot study (P 426), two extended-release formulations were designed by computations (batch No. G224X065 and G224X096) and their expected performance was confirmed by in vitro experiments. The formulations fulfilled the requirement to be dissimilar to the formulation to be marketed and to each other (according to CPMP/QWP/604/96).

Figure 4: Dissolution profiles of dissimilar batches

The two additional extended-release formulations and the formulation to be marketed (G224X085) were investigated in vivo in a pivotal IVIVC study. The open, randomized, balanced, single-dose, cross-over study was conducted in 12 healthy male volunteers under fasting conditions. The washout period lasted 2 weeks.

The hypothetical in vivo dissolution profiles were compared with the in vitro dissolution profiles by determining the times related to identical amounts dissolved under in vitro and in vivo conditions. The maximal limits for in vitro release at different time points all resulted in a difference in the predicted in vivo AUC and C\text{max} of less than 20 %.

P 701: Dose proportionality and absolute bioavailability of extended-release propiverine after oral administration of a single dose were determined in a double-blind, randomized, double-dummy, five-period cross-over study in 10 healthy volunteers. The following treatments were administered:

- Propiverine 15 mg i.v., reference treatment, 3 mg/ml solution, batch no 708034-090299
- Propiverine ER 10 mg capsule, batch no 0300040
- Propiverine ER 15 mg capsule, batch no 0200040
- Propiverine ER 30 mg capsule, batch no 0100040
- Propiverine ER 45 mg capsule, batch no G224X085

Study drug was administered under fasting conditions in 5 single doses with intervals of at least 7 days. Capsules were swallowed with 200 mg tap water. Intravenous solution was injected within 5 minutes.

Serum concentrations of propiverine and of its main metabolite propiverine N-oxide (P4NO) before and 1, 2, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 72, 96 h after oral
administrations and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 72 h after intravenous administration were determined. The amount excreted into urine (0-96 h) was determined.

Determination of accommodation, papillary response to flash light, and salivation before and 2, 4, 6, 8, 10, 12, 15, 24, 30, 36, 48 h after administration was performed to compare pharmacodynamics.

Analytical methods
Propiverine and P4NO plasma concentrations were determined with the LS-MS/MS assay, lower limit of quantification in plasma was 0.78 ng/ml (CV=13.4%) for propiverine and 3.9 ng/ml (CV=6.1%) for P4NO. Plasma samples were prepared using the solid phase extraction. Quadratic regression analysis was used to calculate propiverine and P4NO concentrations in unknown samples. Calibration curve ranged from 0.78 ng/ml to 200.0 ng/ml for propiverine and from 3.9 ng/ml to 1000.0 ng/ml for P4NO.

None of the pre-dose samples contained detectable levels of propiverine, indicating that the length of the washout period was adequate.

Results
Plasma concentration-time profiles for propiverine are presented in Figure 5 below.

![Figure 5](image)

Figure 5: Serum concentrations-time curves of propiverine after intravenous administration and after oral administration of different doses of propiverine hydrochloride given in multi-unit capsules in 10 healthy volunteers. Geometric means are given.

The pharmacokinetic parameters for propiverine and for P4NO are indicated in the tables below.
The study results revealed that the pharmacokinetics of extended-release propiverine in oral doses between 10 and 45 mg is dose-independent. Propiverine was slowly absorbed, the extent of absorption was about 60%.

Table 2: Pharmacokinetic characteristics of propiverine N-oxide after intravenous administration and after administration of different oral doses of extended release propiverine hydrochloride in 10 healthy volunteers. Geometric means and geometric standard deviations are given for all characteristics except $t_{\text{max}}$ for which arithmetic means and standard deviations are listed.
The pharmacokinetics of the metabolite was linear over the studied dose range. Standardised AUC and $C_{\text{max}}$ (normalised to 15 mg) of propiverine are presented below.

![Graph showing linear correlation between AUC and dose](image1)

![Graph showing linear correlation between Cmax and dose](image2)

**Table 3:** AUC and $C_{\text{max}}$ of propiverine (standardised to 15 mg propiverine hydrochloride po) after intravenous administration and after administration of different oral doses of extended release propiverine hydrochloride in 10 healthy volunteers. Geometric means and geometric standard deviations are given.

<table>
<thead>
<tr>
<th>administration route</th>
<th>oral</th>
<th>intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>dose [mg]</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>AUC$_{\text{t-\infty}}$ [(ng*h)/ml]</td>
<td>544 (218, 1357)</td>
<td>638 (423, 963)</td>
</tr>
<tr>
<td>$C_{\text{max}}$ [ng/ml]</td>
<td>27.2 (16.9, 43.8)</td>
<td>27.6 (21.5, 35.5)</td>
</tr>
</tbody>
</table>

**Results for pharmacodynamics**

Propiverine in a dose of 15 mg iv and in single oral doses between 10 and 45 mg did not significantly influence accommodation, pupil functions (diameter, latency, amplitude, duration of the reaction) after flash-light and salivation.
Safety
Safety measurements revealed the typical spectrum of the expected adverse drug reactions of a drug with anticholinergic properties such as dry mouth, headache, tiredness and disturbance of accommodation.

Comment:
The PK study conducted confirmed dose-linearity of the propiverine ER formulation. Absolute bioavailability of propiverine from the ER formulation was 60%.

P 703: Food-drug interaction of propiverine was investigated in a randomised, open, four-way crossover study (including the food interaction with the IR formulation). For the purpose of this report, only results for the extended-release formulation were presented. This study was submitted and has been assessed during the Marketing Authorisation of the 30 mg extended release formulation. Reference is made to PL 15072/0006 (MRP UK/H/917/01).

A single dose of 45 mg propiverine (G224X085) was administered after fasting or after a high fat content meal. 26 subjects were enrolled into the study. There were two drop-outs during this study. PK parameters and relative bioavailability were determined.

<table>
<thead>
<tr>
<th>Test product, dose, administration route and batch numbers (Report no. [P] 703 continued):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propiverine HCl, 2x15mg coated tablets immediate release, (usual sales formulation, Miconorm®, manufactured by Apogepha GmbH), Batch No.: 002061 (IR formulation, after meal), orally administered.</td>
</tr>
<tr>
<td>Propiverine HCl, 45 mg capsules, extended release (formulation under development, contract manufacturer), Batch No.: G224x085, (ER formulation, after meal), orally administered</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference therapy, dose, administration route and batch numbers:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propiverine HCl, 2x15mg coated tablets immediate release, (usual sales formulation, Miconorm®, manufactured by Apogepha GmbH), Batch No.: 002061 (IR formulation fasting), orally administered .</td>
</tr>
<tr>
<td>Propiverine HCl, 45 mg capsules, extended release (formulation, contract manufacturer), Batch No.: G224x085; (ER formulation, fasting), orally administered</td>
</tr>
</tbody>
</table>

Washout period between treatment days was at least 2 weeks.

In study periods with immediate release formulation, blood for the determination of drug concentrations was drawn at: 0 (= prior to administration), 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 24, 36, 48, 60, and 72 hours after administration. In study periods with extended release formulation, blood for the determination of drug concentrations was drawn at: 0 (= prior to administration), 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 30, 36, 48, 60, 72, 84, 96 hours after administration.

For the determination of drug concentrations, urine collection was performed in all study periods at (during): 0 (blank urine), 0-3, 3-6, 6-12, 12-24, 24-48, 48-72 after administration.
Analytical methods
Propiverine and its main metabolite P4NO concentrations were determined in the laboratory.

**PHARMACOKINETIC RESULTS**
Mean Propiverine-HCl (P4) concentration profiles (full profiles (upper graph) and Day 1 profile (lower graph))
The results of the pharmacokinetic evaluation of the propiverine profiles under fasting conditions and after meal indicate no significant difference.

Conclusions
There was no food effect for extended-release formulation.

Applicant’s conclusion on biopharmaceutics:
Based on the data presented it can be concluded that the pharmacokinetics of new extended-release formulation proposed for marketing approval are well-characterized according to the current CPMP guidance:

- The rate and extent of absorption are established. The extent of absorption is similar for the marketed IR formulation and the ER formulation proposed for marketing approval (P 426, P 506, 1).
- Fluctuations in drug concentrations are smaller for the ER formulation proposed for marketing approval compared to the marketed IR formulation (P 506, 1).
- Variability in pharmacokinetics arising from the drug formulation are predictable (P 702).
- Dose proportionality is established (P 701).
- Factors influencing the performance of the modified drug formulation: The food drug interaction was assessed, there is no food effect for the final ER formulation (P 703).
- The risk of unexpected release characteristics was examined in vivo and in vitro, no such incidence was observed (P 702, P 426, P 506, 1, P 701, P 703).

Overall Conclusion on Biopharmaceutics:

The biopharmaceutical development programme has followed the EMEA guidance “Note for Guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation)”. The Applicant has conducted three pivotal PK studies, addressing the dose-linearity, food effect and PK at steady state with the ER formulation.

The studies showed that the extent of absorption, in terms of AUC_{0-24h}, from the ER formulation compared with the IR formulation was similar when given in equivalent daily doses. The fluctuation in drug concentrations was similar as estimated from the PTF, C_{av}, C_{min} and C_{max}, all fell within the standard bioequivalence criteria. The inter-individual variability of propiverine PK after the administration of ER was comparable to that of the IR formulation. The PK of propiverine was linear in the dose range of 10 mg to 45 mg after the administration of ER formulations. The effect of food on the release of propiverine from ER formulation was investigated and no food effect was detected. The ER formulation contains 45 mg of propiverine, therefore the once daily administration is equivalent to the 15 mg IR t.i.d.. The possibility of unexpected release and dumping effect was studied in multiple dose

<table>
<thead>
<tr>
<th>Mean cumulative amounts of metabolites (N=24) excreted into urine within 72 hours after administration of the extended release formulation</th>
<th>Fasted</th>
<th>after meal</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>M23 (mg)</td>
<td>3.12 ± 1.05 / 2.96</td>
<td>3.43 ± 0.81 / 3.33</td>
<td>1.13</td>
</tr>
<tr>
<td>P4NO (mg)</td>
<td>0.96 ± 0.25 / 0.93</td>
<td>1.21 ± 0.23 / 1.18</td>
<td>1.29</td>
</tr>
<tr>
<td>PONO (mg)</td>
<td>1.94 ± 0.40 / 1.90</td>
<td>2.17 ± 0.38 / 2.13</td>
<td>1.12</td>
</tr>
</tbody>
</table>
study. No additional peaks, indicating unexpected release or dumping effect, were revealed.

3.5 Clinical Efficacy

3.5.1 NEUROGENIC DETRUSOR OVERACTIVITY (NDO)

3.5.1.1 Pivotal Clinical Trial (Study ID: P 997)

The study was conducted in compliance with the GCP. The Guideline on Neurogenic Lower Urinary Tract Dysfunction issued by the European Association of Urology was taken into account when designing the study.

**Study design:** The efficacy and safety of the new 45 mg ER capsule proposed for marketing approval was assessed in a randomised, double-blind, double-dummy, parallel group, multi-centre clinical trial.

**Study procedures:** The study comprised two visits: Visit 1 (day -1) and Visit 2 (day 21). After a baseline visit, the patients were treated for 21 days with propiverine IR (15 mg t.i.d.) or propiverine 45 mg ER once daily. Assessments of efficacy and tolerability were made at the first study visit to obtain baseline measurements and at the second study visit to obtain end of treatment values.

**Diagnosis:** Male or female Caucasian patients ≥18 years ≤70 years of age with neurogenic detrusor overactivity (occurrence of reflex detrusor contractions). This assessment was based on urodynamic parameters.

The **main criteria for inclusion** were:

- signed informed consent
- occurrence of reflex detrusor contractions
- reflex volume of ≤250 mL
- intact reflex arcs in the area of segments S2-S4.

Efficacy measurements comprised urodynamic filling cystometry, state of well-being questionnaire incontinence situation, and final evaluation of efficacy of study medication by the investigator and the patient.

As primary efficacy outcome reflex volume, defined as volume at "starting of first hyperreflexive detrusor contraction" had been chosen because it reflects both treatment aims in patients with neurogenic detrusor overactivity:

- Reduction of intravesical pressure in order to minimize or even eliminate complications of the upper urinary tract
- Achievement of continence

The primary criterion of efficacy was the change from baseline in reflex volume, defined as the volume at the first uninhibited bladder contraction determined by cystometric analysis. The primary study objective was to demonstrate non-inferiority of the ER formulation compared to the IR formulation, whereby non-inferiority was pre-defined as a treatment group difference of ≤25 mL in change from baseline of reflex volume. Change from baseline in reflex volume was analyzed in the PP
population using an analysis of covariance (ANCOVA) model with treatment group and baseline value as explanatory variables.

**Statistical analysis plan:** Due to the fact of missing data for propiverine hydrochloride with regard to its effects on the reflex volume an adaptive interim analysis (Bauer and Köhne, 1994) was planned after enrolment and completion of 60 patients to allow for a sample size re-estimation.

**Patient disposition and demographics:** Sixty-six patients, 33 in each treatment group were screened, randomized and treated. One patient from the IR group was lost to follow up after the baseline visit. No other patient was withdrawn from the study. Thus, 32 patients were included in the ITT population in the IR group and 33 patients in the ER group.

3 patients from the IR group and 2 patients from the ER group were excluded from PP population, all of them due to major differences from standard cystometry filling rates, i.e. filling rate cystometry not 20 ml/min, the actual filling rates recorded were for Subject 1 - at visit 2=9ml/min; for Subject 5 - at visit 1=38ml/min; for Subject 6 at visit 1=2ml/min.

Reflex volume, leak point pressure, leak point volume, maximum detrusor pressure, maximum cystometric capacity and bladder compliance were determined by performing an urodynamic examination (filling cystometry).

**Comment:**
The exclusion of three patients due to the non-standard cystometry filling rates is not endorsed. If the Applicant was of the opinion that these patients were not eligible for the study, it should have been specified under the inclusion/exclusion criteria.

The sample size was estimated for the primary endpoint reflex volume (difference to baseline). Since no reliable data on reflex volume from a propiverine hydrochloride study could be used, the data of cystometric capacity at first urge from a similar study (Mürtz G et al, 2001) were used for the sample size estimation. The cystometric capacity at first urge (difference to baseline) was 80.7 mL with a standard deviation of 108.7 mL in the Propiverine hydrochloride group. With a maximum difference δ=25 (mL) (between pre-post differences of reflex volume) for equivalent efficacy to standard treatment a sample size of 297 evaluable patients per group (total 594) was calculated (one-sided test, \( \alpha = 0.025 \) and \( \beta = 0.20 \)).

With an assumed 20% rate of drop-outs, a total of 714 patients were to be entered into the study if no interim analysis was made. Even though the algorithm described by Bauer and Köhne (1994) allowed for a continuation of the study according to the results of the interim analysis, the sponsor decided to discontinue the study as the number of patients needed to demonstrate non-inferiority according to the sample size re-estimation would have been excessive: According to the algorithm used in the study, a total of 938 evaluable patients per treatment arm would have been necessary in the second stage of the study.

The approach used by the Applicant, namely reduction of the sample size due to the excessive number of patients needed to prove non-inferiority, is not endorsed. The Applicant’s pre-specified criterion for non-inferiority was the difference of ≤25 mL in
change from baseline of reflex volume between the treatment groups. However, the 95%CI for the difference were not specified. In order to show that the clinical efficacy of the ER formulation is not inferior to the IR formulation the study should have been powered accordingly. The large sample size needed to prove the non-inferiority is attributable to the very large inter-individual differences in treatment effect.

Thus, 29 patients were included in the PP population in the IR group and 31 patients in the ER group. In the IR group of the PP population, the mean age was 40.5 years; 19 (65.5%) patients were male and 10 (34.5%) were female. In the ER group, the mean age was 42.2 years and 18 (58.1%) patients were male and 13 (41.9%) were female. The median time since manifestation of neurogenic detrusor overactivity was 5.1 years.

**Efficacy assessment:**

| Table 15: Summary of Reflex Volume (mL) - Central Evaluation (PP Population) |
|-----------------------------|-----------------------------|-----------------------------|
| Category                    | Statistic                  | Immediate Release (N = 29)  | Extended Release (N = 31) |
| Baseline (Visit 1)          | n                          | 29                         | 31                         |
| Mean (SD)                   | 100.9 (74.4)               | 89.8 (31.4)                |
| Median                      | 88.0                       | 88.0                       |
| Min - Max                   | 9 to 236                   | 0 to 238                   |
| End of Treatment            | n                          | 29                         | 31                         |
| Mean (SD)                   | 202.9 (112.1)              | 180.3 (104.7)              |
| Median                      | 213.0                      | 161.0                      |
| Min - Max                   | 5 to 400                   | 25 to 400                  |
| Change from baseline at end of treatment | n                      | 29                         | 31                         |
| Mean (SD)                   | 102.0 (35.2)               | 90.5 (32.1)                |
| Median                      | 103.0                      | 78.0                       |
| Min - Max                   | -33 to 295                 | -66 to 294                 |

In both treatment groups, the mean difference between the baseline and after 21-days treatment was significant for the PP population:
IR pre 100.9 mL post 202.9 mL p<0.0001
ER pre 89.8 mL post 180.3 mL p<0.0001

and for the ITT population:
IR pre 102.5 mL post 215.4 mL p<0.0001
ER pre 91.9 mL post 178.1 mL p<0.0001

**Primary endpoint:** The mean improvement in reflex volume from baseline was 102.5 mL in the IR group and 90.1 mL in the ER group of the PP population. The mean treatment group difference ER- IR was -12.4 mL with a 95% confidence interval (CI) from -58.9 mL to 34.0 mL. The one-sided p-value for the test against the hypothesis ER - IR = -25 mL was 0.2952.
The results on primary endpoint indicated slightly better response with the IR formulation, however the 95%CI was very wide.

**Secondary endpoints**

Mean secondary urodynamic parameters showed the therapeutic effects (ITT-population):

- Leak point volume / max. cystometric capacity increased in both groups:
  
  IR pre 134.7 mL post 239.2 mL p<0.0001  
  ER pre 107.9 mL post 200.9 mL p<0.0001  

- Maximum detrusor pressure decreased:
  
  IR pre 63.8 cm H2O post 41.2 cm H2O p=0.0034  
  ER pre 67.9 cm H2O post 45.4 cm H2O p<0.0001  

There was an increment in post void residual, which was expected in these patients exposed to anticholinergic treatment. There was no remarkable difference between the ER and the IR group.

The results were similar for the PP population.

Efficacy based on urodynamic parameters is reflected in the clinical parameters, e.g. incontinence:

- Incontinence, as reported by the patients during the 21-day treatment period:
  
  IR pre 79.3% post 65.5% p=0.134  
  ER pre 80.6% post 41.9% p=0.001  
  IR versus ER p=0.041 (PP population).  

Results were similar for the ITT population:

IR pre 81.3% post 65.6% p=0.074  
ER pre 81.8% post 45.5% p=0.001  
IR versus ER p=0.88 (ITT population).

---

<p>| Table 16: Analysis of Covariance of the Primary Efficacy Endpoint (PP Population) |</p>
<table>
<thead>
<tr>
<th>Change in reflex volume (mL) from baseline to end of treatment (central evaluation)</th>
<th>Immediate Release (N = 29)</th>
<th>Extended Release (N = 31)</th>
<th>Extended Immediate Release</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>29</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Least Squares Mean</td>
<td>102.5</td>
<td>90.1</td>
<td>-12.4</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(69.2; 135.8)</td>
<td>(57.8; 122.3)</td>
<td>(-58.9; 34.0)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.2962</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Estimated from an ANCOVA model with treatment as fixed effect and baseline value as covariate  
2 Non-inferiority margin of 25 mL was subtracted from the Immediate Release measurements at EOT
Despite the fact that both IR and ER formulations showed statistically and clinically significant differences between the baseline and 21-days of treatment, the treatment response for the ER formulation on secondary endpoints was constantly lower than for IR formulation. This was in line with the results on primary endpoint.

**State of Well-Being Questionnaire:** Patients had to mark their current state of well-being on a 100 mm line at each study visit (0 mm = worst state, 100 mm = best state). Mood, level of stress, and productiveness were improved in both treatment groups. The p-values of a Wilcoxon Rank sum test for difference in well-being between treatment groups were 0.6428 for mood, 0.8089 for level of stress, and 0.5267 for productiveness.

**Concomitant treatment:** For prevention of urinary tract infections antibiotic therapy was explicitly allowed and had to be documented in the CRF. The patient had to be free of urinary tract infections at the time of urodynamic examination. 42% of patients in both treatment arms received ciprofloxacin.

**The Applicant’s conclusions:**
APOGEPHA Arzneimittel GmbH has conducted a clinical study with the new 45 mg ER formulation in patients with neurogenic detrusor overactivity.

- Appropriate dynamic endpoints were defined having an established relationship to clinical efficacy.
- The outcome measures are sensitive with respect to the underlying disease conditions. A high between-subject variability has to be taken into account.
- The definition of a reasonable non-inferiority margin is difficult if not impossible in the intended indication bearing in mind that neurogenic detrusor overactivity is a rare disease.
• A placebo arm was not included in the study because there is no placebo effect (see meta-analysis).
• In the pivotal study P 997, the median time since manifestation of neurogenic detrusor overactivity was 5.1 years (Q1: 2.2 years, Q3: 7.8 years). Spontaneous improvement during the 3-week study duration is therefore unlikely.

**Supportive data** are contained in two double-blind, controlled clinical trials conducted to support the licensure of 15 mg tablets. Both studies included patients with NDO. Patients were treated with 15 mg propiverine t.i.d. (60 patients in P765, 70 patients in P691) Comparator drugs were placebo (P765, for 14 days) and oxybutynin (P691, 5 mg x 3 for three weeks).

**Comment**
The Applicant’s justification is not sufficient to prove that the ER is non-inferior to the IR formulation. However, taken into account that

- the neurogenic detrusor overactivity is a rare disease,
- the sample size required to prove non-inferiority is large due to the wide inter-individual variation in treatment response,
- the 15 mg IR tablet three times daily has been approved for this indication,
- the biopharmaceutics programme submitted proved that the 15 mg IR tablets t.i.d. were interchangeable with the 45 mg ER (all PK parameters within the standard BE criteria, including Cmax, Cmin and PTF) and the daily dose of 45 mg is an approved posology, therefore, the lack of proper clinical efficacy study is acceptable. This is further supported that the 30 mg ER tablets approved are interchangeable with the 15 mg IR b.i.d., and the PK of propiverine ER tablets is linear over the dose range of 10mg - 45 mg.

The ER with once daily dosing is an alternative to the IR t.i.d. regimen and may improve treatment compliance. However, the SmPC of the 45 mg ER tablets has to clearly state that the starting dose of propiverine is 15 mg twice a day.

According to the Points to Consider on the Clinical Requirements of Modified Release Products Submitted as a Line Extension of an Existing Marketing Authorization (CPMP/EWP/1875/03/Final, London 2003), generally additional comparative clinical data are needed for modified release products. However, the extent of data depends on the condition studied and on the plasma concentration – effect relationship. The pivotal clinical study submitted by the Applicant does not meet the requirements for non-inferiority study in this condition. The biopharmaceutics programme submitted does explicitly show that the plasma concentration profile of IR t.i.d. at steady state is similar to the ER once daily. No dumping effect was revealed, the fluctuation in serum concentrations was similar (Cmax, Cmin, PFT within the standard BE criteria).

### 3.5.1.2 Meta-analysis of data in NDO

As a result of the scientific advice, the MHRA proposed a meta-analysis including historical placebo data. A meta-analysis evaluating two earlier controlled studies with the propiverine IR formulation in patients with NDO (P 765 Part 3 and 4; P 691) as well as results from P 997 has been performed, see P 1154. Results were given in module 2.7.3.3.
The pivotal study P 997 was evaluated in a meta-analysis together with the two supportive studies given above. The meta-analysis has the identifier P 1154. Pertinent results are presented below.

**Table 4: Demographic data (ITT population): All studies**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category/Statistic</th>
<th>Prop. IR (N = 147)</th>
<th>Prop. ER (N = 33)</th>
<th>Oxybut. (N = 52)</th>
<th>Placebo (N = 53)</th>
<th>Total (N = 235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>147</td>
<td>33</td>
<td>52</td>
<td>53</td>
<td>285</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45 (30.6)</td>
<td>14 (42.4)</td>
<td>14 (28.9)</td>
<td>21 (39.6)</td>
<td>84 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>36.3 (14.8)</td>
<td>40.9 (16.9)</td>
<td>36.0 (14.5)</td>
<td>29.3 (10.9)</td>
<td>35.5 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>32</td>
<td>35</td>
<td>33</td>
<td>27</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.7 (3.9)</td>
<td>23.5 (4.3)</td>
<td>23.7 (3.8)</td>
<td>22.9 (3.5)</td>
<td>23.5 (3.6)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>22.4</td>
<td>23.3</td>
<td>24.0</td>
<td>23.3</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Cap. 1st det. contr./Reflex vol., mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>131.1 (96.1)</td>
<td>91.9 (66.1)</td>
<td>---</td>
<td>148.4 (90.7)</td>
<td>127.6 (90.5)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>110.5</td>
<td>60</td>
<td>---</td>
<td>150</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>Max. cystom. capacity, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>210.7 (123.8)</td>
<td>107.9 (99.7)</td>
<td>170.9 (72.4)</td>
<td>296.4 (151.3)</td>
<td>208.5 (127.1)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>200</td>
<td>95</td>
<td>160</td>
<td>290</td>
<td>187</td>
<td></td>
</tr>
<tr>
<td>Max. detrusor press., cmH₂O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.5 (40.2)</td>
<td>67.9 (30.5)</td>
<td>68.8 (37.3)</td>
<td>91.7 (37.2)</td>
<td>71.7 (39.1)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>60.5</td>
<td>65</td>
<td>66.5</td>
<td>90.3</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

The cystometric data of the three studies were pooled. An indirect comparison of propiverine ER and placebo is based on two of these studies, P 765 and P 997. An ANCOVA model was applied to the change from baseline in the cystometric endpoints with treatment and study as fixed effects and baseline value as a covariate.

In the pooled analysis of reflex volume, the superiority of propiverine ER compared to placebo was not statistically significant. However, maximum cystometric capacity and maximum detrusor pressure showed significant differences between propiverine ER and placebo.

**Table 5: Adjusted change from baseline (ANCOVA) in cystometric data, ITT population: Meta-analysis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Statistic</th>
<th>Propiverine ER (N = 33)</th>
<th>Placebo (N = 53)</th>
<th>Propiverine ER - Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder capacity at first detrusor contraction / Reflex volume (mL)</td>
<td>n</td>
<td>33</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LSm</td>
<td>61.9</td>
<td>27.7</td>
<td>34.1</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(22.8; 100.9)</td>
<td>(-7.7; 63.2)</td>
<td>(-27.0; 95.2)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td></td>
<td>0.2715</td>
</tr>
<tr>
<td>Max. cystom. capacity (mL)</td>
<td>n</td>
<td>33</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LSm</td>
<td>89.1</td>
<td>4.5</td>
<td>84.6</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(42.0; 136.2)</td>
<td>(-43.7; 34.8)</td>
<td>(25.8; 161.4)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td></td>
<td>0.0070</td>
</tr>
<tr>
<td>Maximum detrusor pressure (cmH₂O)</td>
<td>n</td>
<td>33</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LSm</td>
<td>-23.4</td>
<td>7.2</td>
<td>-30.6</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(-35.3; -11.6)</td>
<td>(-2.7; 17.1)</td>
<td>(-47.7; -13.5)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td></td>
<td></td>
<td>0.0005</td>
</tr>
</tbody>
</table>
3.5.2 IDIOPATHIC DETRUSOR OVERACTIVITY (overactive bladder)

A total daily dose of 45 mg (15 mg t.i.d.) is covered by the current SmPC for the 15 mg IR formulation. Taking into account dose-linearity and the proof of efficacy of the 30 mg ER capsule in a placebo-controlled, non-inferiority trial, no further study was conducted with the 45 mg ER capsule in patients with overactive bladder syndrome.

Reference is made to Mictonorm XL 30mg Modified-Release Capsules, PL 15072/0006 (MRP UK/H/0917/01). Approval was based on the following pivotal study and supportive studies as identified by Study ID:

- pivotal clinical trial P 659,1
- supportive studies P 281; P 517; P 269; P 661,1; P 088; P 095; P 106

As already pointed out, the 30 mg ER capsule has been granted marketing approval for the treatment of patients with overactive bladder syndrome. The majority of patients can be successfully treated with a daily dose of 30 mg propiverine. However, according to clinical experience about 35% patients require a higher dose of 45 mg per day.

3.6 Safety

The safety of the 45 mg ER capsule was assessed in patients who participated in the double-blind, controlled study P 997.

A total of 66 patients were randomised, 33 per treatment group (safety population).

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Immediate Release (N = 33)</th>
<th>Extended Release (N = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any adverse event, n (%)</td>
<td>18 (48.5)</td>
<td>12 (36.4)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Patients with serious non-fatal adverse events, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Patients with any adverse event leading to withdrawal, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Patients with any treatment related adverse event, n (%)</td>
<td>14 (42.4)</td>
<td>12 (36.4)</td>
</tr>
</tbody>
</table>
The total number of AEs was high in all treatment groups, including the placebo groups. The increase in daily dose from 30 mg to 45 mg is accompanied by a clear increase in the overall number of AEs. However, a clinically remarkable increase in specific adverse effects is not observed but rather an increase across SOCs and preferred terms.

Safety is reviewed in the clinical overview. No new safety issues have been identified. The safety profile of propiverine hydrochloride is well-known through its extensive

---

**Table 5: Adverse events by MedDRA SOC and Preferred Term**

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Immediate Release</th>
<th>Extended Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall Related¹</td>
<td>Overall Related¹</td>
</tr>
<tr>
<td>All Patients (N = 33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>16 (48.5)</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>11 (33.3)</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>8 (24.2)</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>Gastrointestinal motility disorder</td>
<td>8 (24.2)</td>
<td>8 (24.2)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>3 (9.1)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

**Male Patients (N = 22)**

| Any adverse event         | 12 (54.5)         | 11 (50.0)         |
| Gastrointestinal disorders| 9 (40.9)          | 9 (40.9)          |
| Dry Mouth                 | 8 (36.4)          | 8 (36.4)          |
| Gastrointestinal motility disorder | 1 (4.5) | 1 (4.5) |
| Nervous system disorders  | 0 (0.0)           | 0 (0.0)           |
| Dizziness                 | 0 (0.0)           | 0 (0.0)           |
| Headache                  | 2 (9.1)           | 0 (0.0)           |
| Eye disorders             | 2 (6.1)           | 0 (0.0)           |

**Female Patients (N = 11)**

| Any adverse event         | 4 (36.4)          | 3 (27.3)          |
| Gastrointestinal disorders| 2 (18.2)          | 2 (18.2)          |
| Dry Mouth                 | 0 (0.0)           | 0 (0.0)           |
| Gastrointestinal motility disorder | 2 (18.2) | 2 (18.2) |
| Nervous system disorders  | 0 (0.0)           | 0 (0.0)           |
| Dizziness                 | 0 (0.0)           | 0 (0.0)           |
| Headache                  | 2 (9.1)           | 0 (0.0)           |
| Eye disorders             | 1 (4.5)           | 0 (0.0)           |

¹ Adverse events with certain, probable, possible, conditional or unassessable relationship to study medication

**Table 6: Incidence of AEs; 30 mg vs 45 mg daily dose**

<table>
<thead>
<tr>
<th>Daily dose (mg)</th>
<th>30 IR</th>
<th>45 IR</th>
<th>30 ER</th>
<th>45 ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs &amp; Body system</td>
<td>Propiv</td>
<td>Placebo</td>
<td>Propiv</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>460</td>
<td>267</td>
<td>457</td>
<td>354</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>334</td>
<td>104</td>
<td>631</td>
<td>288</td>
</tr>
<tr>
<td>Body as a whole - general disorders</td>
<td>18</td>
<td>5.4%</td>
<td>4</td>
<td>3.3%</td>
</tr>
<tr>
<td>fatigue</td>
<td>5</td>
<td>1.5%</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>influenza or (-like illness)</td>
<td>2</td>
<td>0.6%</td>
<td>0</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
use in clinical practice. The adverse events that can be expected are listed in the SmPC.

### 3.7 Post marketing experience

Propiverine hydrochloride has a well-recognised efficacy and an acceptable level of safety in the indications approved for Mictonorm XL 45 mg Modified-Release Capsules.

**Pharmacovigilance system**
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

**Risk management plan**
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

**Expert report**
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory summary of the clinical part of the dossier.

**Product literature**
All product literature (SmPC, PIL and labelling) is medically satisfactory.

**CLINICAL CONCLUSION**
There are no objections to the approval of Mictonorm XL 45 mg Modified Release Capsules from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Mictonorm XL 45 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of these type.

EFFICACY
Clinical pharmacokinetics and pharmacodynamics of propiverine are well-known; reference is made to PL 15072/0002 (MRP UK/H/0271/01) and PL 15072/0006 (MRP UK/H/0917/01). The application is supported by a series of pharmacokinetic and clinical efficacy studies as detailed in this report. Six bioavailability studies were performed in support of this application.

For the indication in neurogenic detrusor overactivity (NDO), the pivotal clinical trial was Study P 997. The conclusion from this study was that the ER with once daily dosing is an alternative to the IR t.i.d. regimen and may improve treatment compliance.

For the indication in idiopathic detrusor overactivity (overactive bladder), reference is made to Mictonorm XL 30mg Modified-Release Capsules, PL 15072/0006 (MRP UK/H/0917/01), whose approval was based on the following pivotal study and supportive studies as identified by Study ID:

SAFETY
No new or unexpected safety concerns arise from this application.

The SmPC, PIL and product labelling contain appropriate safety information.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with propiverine hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be acceptable. A Marketing Authorisation should be granted.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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