SUMMARY OF PRODUCT CHARACTERISTICS

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 with known effect: Lactose monohydrate (8.5 mg)
For the 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

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 a day. 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 dose regimen for the elderly (see section 5.2).

Paediatric population: Due to a lack of data, this product should not be used in children.

Caution should be exercised and physicians should monitor patients carefully for side effects in the following dispositions (see sections 4.4, 4.5, 5.2).

Use in renal impairment

In 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 hydrochloride is 30 mg. Therefore, Mictonorm XL 45 mg modified-release capsules are not recommended in patients with severe renal failure.

Use in hepatic impairment

In patients with mildly impaired hepatic function, there is no need for dose adjustment; however, treatment should proceed with caution. No studies have been performed to investigate the use of propiverine in patients with moderately or severely impaired hepatic function. Its use is therefore not recommended in these patients (see section 5.2).

Patients receiving concomitant treatment with drugs that are potent inhibitors of CYP 3A4 combined with methimazole

In patients receiving drugs that are potent flavin-containing monooxygenase (FMO) inhibitors such as methimazole in combination with potent CYP 3A4/5 inhibitors treatment should start with a dose of 15 mg per day. The dose may thereafter be titrated to a higher dose. However, caution should be exercised and physicians should monitor these patients carefully for side effects (see sections 4.5, 5.2).

Method of administration

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

There is no clinically relevant effect of food on the pharmacokinetics of Mictonorm XL 45 mg modified-release capsules (see section 5.2). Accordingly, there is no particular recommendation for the intake of Mictonorm XL 45 mg 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 listed in section 6.1and in patients suffering from one of the following disorders:

- obstruction of the bowel
- significant degree of bladder outflow obstruction where urinary retention may be anticipated
- myasthenia gravis
- intestinal atony
- severe ulcerative colitis
- toxic megacolon
- uncontrolled angle closure glaucoma

- moderate or severe hepatic impairment
- tachyarrhythmias

4.4 Special warnings and precautions for use

The drug should be used with caution in patients suffering from:
- autonomic neuropathy
- renal impairment (see section 4.2)
- hepatic impairment (see section 4.2)

Symptoms of the following diseases may be aggravated following administration of the drug:
- severe congestive heart failure (NYHA IV)
- prostatic enlargement
- hiatus hernia with reflux oesophagitis
- cardiac arrhythmia
- tachycardia

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

Pollakiuria and nocturia due to renal disease or congestive heart failure, as well as organic bladder diseases (e.g. urinary tract infections, malignancy), should be ruled out prior to treatment.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

- Increased effects due to concomitant medication with tricyclic antidepressants (e. g. imipramine), tranquillisers (e.g. benzodiazepines), anticholinergics (if applied systemically), amantadine, neuroleptics (e. g. phenothiazines) and beta-adrenoceptor agonists (beta-sympathomimetics).
- Decreased effects due to concomitant medication with cholinergic drugs.
- Reduced blood pressure in patients treated with isoniazid.
- The effect of prokinetics such as metoclopramide may be decreased.
- Pharmacokinetic interactions are possible with other drugs metabolised by cytochrome P450 3A4 (CYP 3A4). However, a very pronounced increase of concentrations for such drugs is not expected as the effects of propiverine are small compared to classical enzyme inhibitors (e.g. ketoconazole or grapefruit juice). Propiverine may be considered as weak inhibitor of CYP 3A4. Pharmacokinetic studies with patients concomitantly receiving potent CYP 3A4

inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole) or macrolide antibiotics (e.g. erythromycin, clarithromycin) have not been performed.

- Patients receiving concomitant treatment with drugs that are potent inhibitors of CYP 3A4 combined with methimazole:
  In patients receiving drugs that are potent flavin-containing monooxygenase (FMO) inhibitors such as methimazole in combination with potent CYP 3A4/5 inhibitors treatment should start with a dose of 15 mg per day. The dose may be titrated to a higher dose. However, caution should be exercised and physicians should monitor these patients carefully for side effects (see sections 4.2, 5.2).

4.6 Fertility, pregnancy and lactation

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

Breast-feeding
It is unknown whether propiverine or metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of propiverine or metabolites in milk. A risk to the newborn or infant cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from propiverine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no human data on the effect of propiverine on fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Propiverine may produce drowsiness and blurred vision. This may impair the patient's ability to exert activities that require mental alertness such as operating a motor vehicle or other machinery, or to exert hazardous work while taking this drug.
Sedative drugs may enhance the drowsiness caused by propiverine.

4.8 Undesirable effects

Within each system organ class, the undesirable effects are ranked under heading of frequency using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)

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

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

Immune system disorders
Rare: hypersensitivity

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

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

Eye disorders
Common: accommodation disorder, visual impairment

Cardiac disorders
Rare: tachycardia
Very rare: palpitation

Vascular disorders
Uncommon: decreased blood pressure with drowsiness, flushing

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

Skin and subcutaneous tissue disorders
Uncommon: pruritus
Rare: rash

Renal and urinary disorders
Uncommon: urinary retention, bladder and urethral symptoms

General disorders and administration site conditions
Common: fatigue

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms:
Overdose with the muscarinic receptor antagonist propiverine can potentially result in severe anticholinergic effects. Peripheral and central nervous system disturbances may occur, such as:
- severe dry mouth
- bradycardia, possibly leading to tachycardia in the further course
- mydriasis and accommodation disorder
- urinary retention
- inhibition of intestinal motility
- restlessness, confusion, hallucination, confabulation
- dizziness, nausea, speech disorder, muscular weakness

Treatment:
- In the event of overdose with propiverine the patient should be treated with activated charcoal suspension with plenty amount of water.
- Gastric lavage should only be taken into consideration with protective intubation, use of an oiled tube (dryness of mucosa) and if performed within 1 hour after ingestion of propiverine. Vomiting must not be induced.
- Forced diuresis or hemodialysis is not effective to enhance the renal elimination.
- In case of severe central anticholinergic effects such as hallucinations or pronounced excitation antidote treatment with physostigmine can be attempted.
- Convulsion or pronounced excitation: treatment with benzodiazepines
- Respiratory insufficiency: treatment with artificial respiration
- Urinary retention: treatment with catheterization
- Mydriasis: treatment with pilocarpine eye drops and/or darkening of the patient's room

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G04BD06
Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence

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

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

Pharmacodynamic effects
In animal models propiverine hydrochloride causes a dose-dependent decrease of the intravesical pressure and an increase in bladder capacity.
The effect is based on the sum of the pharmacological properties of propiverine and three active urinary metabolites as shown in isolated detrusor strips of human and animal origin.

5.2 Pharmacokinetic properties

Absorption
After oral administration of Mictonorm XL 45 mg, 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 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, 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 and Mictonorm XL 45 mg:

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

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

		geometric mean (range)
AUC_{0-24h}	[ng·h/ml]	1711 (1079, 2713)
PTF	[%]	109.4 (81.2, 147.5)
C_{av}	[ng/ml]	71 (45.0, 113.0)
C_{max}	[ng/ml]	105 (71, 155)
C_{min}	[ng/ml]	29 (20, 42)
$t_{1/2}$	[h]	20.4 (12.8, 32.3)
t_{max}	[h]	7.3 (SD: ±2.5)

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-containing monooxygenases (FMO) 1 and 3 and leads to the formation of the much less active N-oxide, the plasma concentration of which greatly exceeds that of the parent substance. Four metabolites were identified in urine; three of them are pharmacologically active and may contribute to the therapeutic efficacy. In vitro there is a slight inhibition of CYP 3A4 and CYP 2D6 detectable which occurs at concentrations exceeding therapeutic plasma concentrations 10- to 100-fold (see section 4.5).

Elimination

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

Linearity/ non-linearity

Following oral administration of 10 – 45 mg of propiverine hydrochloride the C_{max} and the $AUC_{0-\infty}$ 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.
No effects on male and female fertility and reproduction behaviour were observed in toxicological studies with rats.
In animal studies, skeletal retardation in the offspring occurred when the drug was administered orally at high doses to pregnant females. In lactating mammals propiverine was excreted into the milk.
There was no evidence of mutagenicity. The carcinogenicity study in mice demonstrated an increased incidence of hepatocellular adenoma and carcinoma in high dose males. In the rat carcinogenicity study hepatocellular adenoma, kidney adenoma and urinary bladder papilloma has been demonstrated in high dose male rats, while in female animals endometrial stromal polyps were increased at the high dose levels. Both the rat and mouse tumours were considered to be species specific and therefore not of clinical relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pellets

Citric acid,
povidone,
lactose monohydrate,
talc,
triethyl citrate,
magnesium stearate,
methacrylic acid–methyl methacrylate copolymer (1:1),
methacrylic acid-methyl methacrylate copolymer (1:2),
ammonio methacrylate copolymer type A,
ammonio methacrylate copolymer type B.

Capsule

Gelatine,
Titanium dioxide E171,
red iron oxide E172,
yellow iron oxide E172.

6.2 Incompatibilities

not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blisters of PVC/PVDC and aluminium foil in cartons of 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112, 168 or 280 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)

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