APOGEPHA

1. NAME OF THE MEDICINAL PRODUCT

Mictonorm® 15 mg Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 15 mg propiverine hydrochloride equivalent to 13.64 mg propiverine.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Lenticular glazing coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Coated tablets for oral application.
The recommended daily doses are as follows:
Adults: As a standard dose one coated tablet (= 15 mg propiverine hydrochloride) twice a day is recommended, this may be increased to three times a day.
Elderly: Generally there is no special dosage regimen for the elderly (see 5.2).
There is no clinically relevant effect of food on the pharmacokinetics of propiverine (see 5.2). Accordingly, there is no particular recommendation for the intake of propiverine in relation to food.
This medicinal product contains 0.61 mg of glucose. Accordingly, a daily dose of 2 coated tablets supplies 1.22 mg of glucose.

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
- pregnant or nursing woman.

4.4 Special warnings and special precautions for use

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

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

Propiverine, like other anticholinergics, induces mydriasis. Therefore, the risk to induce acute angle-closure glaucoma in individuals predisposed with narrow angles of the anterior chamber may be increased. Drugs of this class have been reported to induce or precipitate acute angle-closure glaucoma.
Pollakiuria and nocturia due to renal disease or congestive heart failure as well as organic bladder diseases (e.g. urinary tract infections, malignancy) should be ruled out prior to treatment.
Due to a lack of data Mictonorm® 15 mg Coated Tablets should not be used in children.

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

4.6 Pregnancy and lactation

There are no adequate data from the use of propiverine hydochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
The drug is secreted into the milk of lactating mammals.
Propiverine hydrochloride should not be used during pregnancy and should not be administered to nursing women.

4.7 Effects on ability to drive and use machines

Propiverine hydrochloride may produce drowsiness and blurred vision. This may impair the patient's ability to exert activities that require mental alertness such as operating a motor vehicle or other machinery, or to exert hazardous work while taking this drug.
Sedative drugs may enhance the drowsiness caused by propiverine hydrochloride

4.8 Undesirable effects

Adverse reactions	System organ class (Disorders according to MedDRA)
Very common (>1/10)	
- dry mouth	Gastrointestinal
Common(>1/100, <1/10)	
- accommodation abnormal, accommodation disturbances, vision abnormal	Eye
- constipation	Gastrointestinal
Uncommon (>1/1,000, <1/100)	
- fatigue	General disorders and administration site conditions
- nausea/vomiting	Gastrointestinal
- dizziness	Nervous system
- tremor	Nervous system
- urinary retention	Urinary system
- flushing	Vascular
- decreased blood pressure with drowsiness	Vascular
Rare (>1/10,000, <1/1,000)	
- rash due to idiosyncrasy (propiverine hydrochloride) or hypersensitivity (excipients, e. g. colorant)	Skin and subcutaneous tissue
Very rare (<1/10,000, including isolated reports)	
- palpitation	Cardiac
- restlessness, confusion	Psychiatric

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 infection

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G04B D06
Pharmacotherapeutic group: spasmolytic, anticholinergic

- Mechanism of action

Inhibition of calcium influx and modulation of intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis.
Inhibition of the efferent connection of the nervus pelvicus due to anticholinergic action.

- Pharmacodynamic effects

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

5.2 Pharmacokinetic properties

- General characteristics of the active substance

Propiverine is nearly completely absorbed from the gastrointestinal tract. It undergoes extensive first pass metabolism. Effects on urinary bladder smooth muscle cells are due to the parent compound and three active metabolites as well, which are rapidly excreted into the urine.

▪ Absorption

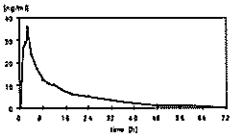
After oral administration of Mictonorm® 15 mg Coated Tablets propiverine is rapidly absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 2.3 hours. The mean absolute bioavailability of Mictonorm® 15 mg Coated Tablets is 40.5 % (arithmetic mean value for $AUC_{0-\infty\ (p.o.)}$ / $AUC_{0-\infty\ (i.v.)}$).

Food intake increases the bioavailability of propiverine (mean increase 1.3fold), but does not significantly affect the maximum plasma concentrations of propiverine or of its main metabolite, propiverine-N-oxide. This difference in bioavailability is unlikely to be of clinical significance and adjustment of dose in relation to food intake is not required.

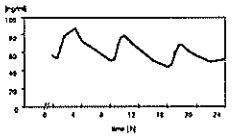
▪ Distribution

After administration of Mictonorm® 15 mg Coated Tablets t.i.d., steady state is reached after four to five days at a higher concentration level than after single dose application ($C_{average}$ = 61 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.

Plasma concentrations of propiverine in 16 healthy volunteers after single and repeated administration of Mictonorm® 15 mg Coated Tablets (t.i.d. for 6 days):



single dose



multiple dose

Steady state characteristics of propiverine following multiple-dose administration to 16 healthy volunteers of Mictonorm®15 mg Coated Tablets (t.i.d. for 6 days):

Dose interval	AUC_{0-t}		PTF		$C_{average}$	
[h]	[ng·h/ml]	CV [%]	[%]	CV [%]	[ng/ml]	CV [%]
0 - 8	515	35	57	16	64	36
8 - 16	460	33	70	25	57	33
16 - 24	421	36	52	39	52	36

CV: coefficient of variation
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; two of them are pharmacologically active and may contribute to the therapeutic efficacy of Mictonorm® 15 mg Coated Tablets.

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). In three studies including a total of 37 healthy volunteers the mean elimination half-life was 14.1, 20.1 and 22.1 hours, respectively.

▪ Linearity/ non-linearity

Pharmacokinetic parameters of propiverine and propiverine-N-oxide following oral administration of 10 - 30 mg of propiverine hydrochloride are linearly related to dose. There are no changes of pharmacokinetics during steady state compared to single dose administration.

- Characteristics in patients

▪ Renal impairment:

Severe renal impairment does not significantly alter the disposition of propiverine and its main metabolite, propiverine-N-oxide, as deduced from a single dose study in 12 patients with creatinine clearance < 30 ml/min. No dose adjustment is to be recommended as long as the total daily dose does not exceed 30 mg (i.e. Mictonorm® 15 mg Coated Tablets given b.i.d.). In case that higher dose (i.e. 45 mg) shall be administered a careful titration of dose is recommended considering anticholinergic effects as a marker for tolerability.

▪ 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 (Mictonorm® 15 mg Coated Tablets t.i.d. for 28 days) 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.

▪ Patients with glaucoma:

Intraocular pressure in patients with open angle glaucoma and in patients with treated (controlled) angle closure glaucoma is not increased by Mictonorm® 15 mg Coated Tablets t.i.d., as demonstrated by two placebo-controlled studies.

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 occured 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 of propiverine and its main metabolites. Carcinogenicity studies in rodents revealed three types of tumors which were considered to be species specific and therefore not of clinical relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, powdered cellulose, magnesium stearate, sucrose, talc, heavy kaolin, calcium carbonate, titanium dioxide (E171), acacia gum, colloidal anhydrous silica, Macrogol 6000, glucose monohydrate, montan wax.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

PVC/aluminum blisters in carton with 7 coated tablets per blister:

28 (4 blisters per carton)
56 (8 blisters per carton)

6.6 Instructions for use and handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

APOGEPHA Arzneimittel GmbH, Kyffhaeuserstrasse 27, 01309 Dresden, Germany
Imported/distributed by: PHARMAFORTE SINGAPORE PTE LTD., 6, Tagore Drive, Tagore Industrial Building #03-11, Singapore 787623

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10. DATE OF REVISION OF THE TEXT

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