APOGEPHA

Mictonorm® 15 mg film-coated tablets

Product Description

White, round, biconvex film-coated tablet of uniform external appearance

Name and strength of active ingredient(s)

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

Excipients with known effect: Each film-coated tablet contains 100.7 mg lactose monohydrate.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence.
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.
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.

Pharmacokinetic properties

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.
Bioequivalence of Mictonorm® 15 mg film-coated tablets with the reference medicinal product Mictonorm® has been demonstrated by an appropriate bioavailability study.
After oral administration of Mictonorm®, propiverine is rapidly absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 2.3 hours. The mean absolute bioavailability of Mictonorm® 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 but adjustment of dose in relation to food intake could be required in patients suffering from impaired renal or hepatic function. Therefore, a regular intake before meals is recommended.
After administration of Mictonorm® 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.
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 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 of Mictonorm®.
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.
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.

Therapeutic indications

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

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

Special warnings and precautions for use

The drug should be used with caution in patients suffering from:
- Autonomic neuropathy
- Renal impairment
- Hepatic impairment

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 medicine.
Due to its high strength Mictonorm® 15 mg film-coated tablets should not be used in children younger than 12 years and adults with a body weight below 35 kg.

Fertility, pregnancy and lactation

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.

Pregnancy

There are no data from the use of propiverine in pregnant women. Studies in animals have shown reproductive toxicity. Mictonorm® 15 mg film-coated tablets 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 Mictonorm® 15 mg film-coated tablets therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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 β-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 and cisapride may be decreased.
  Pharmacokinetic interactions are possible with other drugs metabolised by cytochrome P450 3A4 (CYP 3A4). However, a very pronounced increase of concentrations for such drugs is not expected as the effects of propiverine are small compared to classical enzyme inhibitors (e.g. ketoconazole or grapefruit juice).

Propiverine may be considered as weak inhibitor of CYP 3A4. Pharmacokinetic studies with patients concomitantly receiving potent CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole) or macrolide antibiotics (e.g. erythromycin, clarithromycin) have not been performed.

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

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

Undesirable effects

The following undesirable effects can be associated with the use of propiverine hydrochloride:
Very common: dry mouth
Common: headache, accommodation disorder, visual impairment, constipation, abdominal pain, dyspepsia, fatigue
Uncommon: tremor, dizziness, dysgeusia, decreased blood pressure with drowsiness, flushing, nausea/vomiting, pruritus, urinary retention, bladder and urethral symptoms
Rare: hypersensitivity, tachycardia, rash,
Very rare: restlessness, confusion, palpitation
Not known: hallucination, speech disorder
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.
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 hydrochloride.

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

Recommended dose

The recommended daily doses are as follows:
Adults: As a standard dose one film-coated tablet (=15 mg propiverine hydrochloride) twice daily is recommended, this may be increased to three times daily. Some patients may already respond to a dosage of 15 mg daily.
For neurogenic detrusor overactivity a dose of one film-coated tablet three times daily is recommended. The maximum recommended daily dose is 45 mg.

Paediatric population: Due to a lack of data Mictonorm® 15 mg film-coated tablets should not be used in children.

Elderly: Generally there is no special dosage regimen for the elderly.
Caution should be exercised and physicians should monitor patients carefully for side effects in the following dispositions:

Use in renal impairment
In patients with mild or moderate impairment of renal function, no dose adjustment is required; however, they should be treated with caution. In patients with severely impaired renal function (creatinine clearance < 30 ml/min), the maximum daily dose is 30 mg.

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 contraindicated in these patients.
A high fat meal increases the bioavailability of propiverine. Therefore, propiverine should be taken before meals; especially in patients with renal or hepatic impairment.

Route of administration

Film-coated tablets for oral use.

Nature and contents of container

They are available in PVC/PVDC/aluminium blister packs of 28 or 56 tablets. Not all pack sizes may be marketed.

Special precautions for storage

Store below 30 °C.

Shelf life

5 years.

Manufacturer

Rottendorf Pharma GmbH
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Product Registration Holder:

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