*Date:* 12 October 2020
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*

# Mictonorm

**International non-proprietary name:** propiverinum, propiverini hydrochloridum
**Pharmaceutical form:**
**Dosage strength:** Mictonorm 30 mg, modified-release capsule
**Route(s) of administration:** oral
**Marketing Authorisation Holder:** Labatec Pharma SA
**Marketing Authorisation No.:** 67514
**Decision and Decision date:** approved on 13 August 2020

**Note:**

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.



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## About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

## About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.



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# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADME | Absorption, Distribution, Metabolism, Elimination |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| AUC0-24h | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| Cmax | Maximum observed plasma/serum concentration of drug |
| CYP | Cytochrome P450 |
| ERA | Environmental Risk Assessment |
| GLP | Good Laboratory Practice |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International Nonproprietary Name |
| LoQ | List of Questions |
| MAH | Marketing Authorisation Holder |
| Max | Maximum |
| Min | Minimum |
| N/A | Not applicable |
| NO(A)EL | No Observed (Adverse) Effect Level |
| PD | Pharmacodynamics |
| PIP | Paediatric Investigation Plan (EMA) |
| PK | Pharmacokinetics |
| PopPK | Population PK |
| PSP | Pediatric Study Plan (US-FDA) |
| RMP | Risk Management Plan |
| SwissPAR | Swiss Public Assessment Report |
| TPA | Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21) |



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# 2 Background Information on the Procedure

## 2.1 Applicant's Request(s)

**New Active Substance status**
The applicant requested the status of a new active entity for the active substance propiverine, propiverine hydrochloride of the medicinal product mentioned above.

**Authorisation in accordance with Art. 14 para. 1 a$^{bis}$ TPA**
The applicant requested a simplified authorisation in accordance with Art. 14 para. 1 a$^{bis}$ TPA.

## 2.2 Indication and Dosage

### 2.2.1 Requested Indication

Mictonorm is indicated for symptomatic treatment of aconuresis and/or higher frequency of micturition and imperative urge to urinate in patients with overactive bladder.

### 2.2.2 Approved Indication

Symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder.

### 2.2.3 Requested Dosage

*Usual dosage*
The recommended daily doses are as follows:
*Adults:* The standard recommended dose is one capsule per day (= 30 mg propiverine hydrochloride).

*Dose adjustment / titration*
In patients treated with flavin-containing monooxygenase inhibitors (FMO) such as methimazole in combination with potent inhibitors of CYP 3A4/5, the dosage must be adjusted to 15 mg propiverine hydrochloride per day. This dose can be increased (titration of dosage). The treatment should proceed with caution, and physicians should monitor these patients carefully for undesirable effects.

*Patients with hepatic impairment*
No dose adjustment is required in patients with mild hepatic impairment, but the treatment should proceed with caution. No studies have been performed to investigate the use of propiverine hydrochloride in patients with moderate to severe hepatic impairment.

### 2.2.4 Approved Dosage

(see appendix)

## 2.3 Regulatory History (Milestones)

| | |
|---|---|
| Application | 8 April 2019 |
| Formal control completed | 20 June 2019 |
| List of Questions (LoQ) | 8 October 2019 |
| Answers to LoQ | 12 December 2019 |
| Predecision | 10 March 2020 |
| Answers to Predecision | 11 May 2020 |
| Labelling corrections | 20 May 2020 |
| Answers to Labelling corrections: | 2 July 2020 |



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| | |
|---|---|
| Final Decision | 13 August 2020 |
| Decision | approval |

For the application for the authorisation of the medicinal product Mictonorm, modified-release capsule, Swissmedic has reviewed the quality exclusively on the basis of primary data. The authorisation of Mictonorm, modified-release capsule is based primarily on the medicinal product Mictonorm XL 30 mg, modified-release capsule, which contains the same active substance and has been authorised in the United Kingdom for more than 10 years. Apart from the quality-related aspects for which Swissmedic has conducted an independent scientific review, this SwissPAR refers to the authorisation of the foreign medicinal product Mictonorm XL 30 mg, modified-release capsule.



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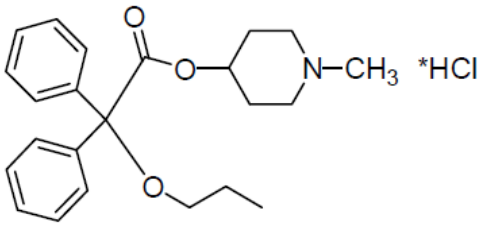
# 3 Quality Aspects

## 3.1 Drug Substance

INN: Propiverine hydrochloride
Chemical name: 2,2-diphenyl-2-(1-propoxy)acetic acid-(1-methylpiperid-4-yl)ester hydrochloride
Molecular formula: $C_{23}H_{30}ClNO_3$
Molecular mass: 403.95
Molecular structure:




The drug substance is a white, crystalline, water-soluble powder with a bitter, burning taste. The drug substance is freely soluble at pH 1-5.8 and slightly to very slightly soluble at pH 6.24-7.22.

The synthesis of propiverine hydrochloride is performed in three steps: (1) Base-catalysed transesterification of benzilic acid methyl ester with 1-methyl-4-hydroxypiperidine by sodium methylate to the purified intermediate 2,2-diphenyl-2-hydroxyacetic acid-(1-methyl-piperid-4-yl) ester. (2) Chlorination of the intermediate to the 2,2-diphenyl-2-chloroacetic acid-(1-methylpiperid-4-yl)ester hydrochloride by thionyl chloride. (3) Etherification of this α-chloroester hydrochloride with 1-propanol to propiverine hydrochloride raw material and recrystallisation of the raw material from 1-propanol.

The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of propiverine hydrochloride.

Propiverine hydrochloride is packed first in a low-density polyethylene bag, second in a polyethylene-coated alu-bag and third in a fibre drum. Appropriate stability data have been generated, resulting in a suitable retest period when packaged in the packaging type described above.

## 3.2 Drug Product

Description and composition: The drug product consists of hard gelatin capsules filled with modified-release pellets. These pellets contain, per capsule, 30 mg of the drug substance propiverine hydrochloride.

Formulation development has been adequately described and justified. Due to the pH-dependent solubility of propiverine hydrochloride, the drug substance has been combined with acidic excipients (citric acid) and sprayed on pellets. These pellets are coated with a modified-release layer followed by a gastro-resistant layer. Process parameters and in-process controls are defined in order to ensure a consistent quality of the finished product.

For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include relevant physicochemical characteristics, identification of the drug substance as well as assay and purity tests.

The finished drug product is packed in a PVC/PVDC/aluminium blister.

Appropriate stability data have been generated in the packaging material for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was



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established. The storage recommendation is “Do not store above 30°C. Store in the original container in order to protect the product from humidity“.

### 3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated



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# 4 Nonclinical Aspects

In accordance with Art. 14 para. 1 a$^{bis-quater}$ TPA, Swissmedic has not reviewed any nonclinical data for the authorisation of the medicinal product Mictonorm, modified-release capsule. The approval of the medicinal product Mictonorm, modified-release capsule is based on the medicinal product Mictonorm XL 30 mg, modified-release capsule, which contains the same active substance and has been authorised in the United Kingdom for more than 10 years.



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# 5 Clinical and Clinical Pharmacology Aspects

For the application for the authorisation of the medicinal product Mictonorm, modified-release capsule, Swissmedic has conducted only a summary review of efficacy and safety. The authorisation of Mictonorm, modified-release capsule is based primarily on the medicinal product Mictonorm XL 30°mg, modified-release capsule, which contains the same active substance and has been authorised in the United Kingdom for more than 10 years. This SwissPAR refers to the authorisation of the foreign comparator medicinal product Mictonorm XL 30 mg, modified-release capsule.

## 5.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.



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# 6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.



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# 7 Appendix

## 7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Mictonorm was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.



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*Placeholder for text approval stamp*

## Mictonorm

The efficacy and safety of Mictonorm modified-release capsules have only been briefly reviewed by Swissmedic. The authorization of Mictonorm modified-release capsules is based on that of Mictonorm XL 30 mg, which contains the same active substance and is authorized in the United Kingdom and the information of which was updated in November 2017.

### Composition

*Active substances*

Propiverinum hydrochloridum

*Excipients*

Pellets
- acidum citricum
- polyvidonum
- lactosum monohydricum 5.7 mg
- talcum
- triethylis citras
- magnesii stearas
- acidi methacrylici et methylis methacrylatis polymerisatum 1:1
- acidi methacrylici et methylis methacrylatis polymerisatum 1:2
- ammonio methacrylatis copolymerum A
- ammonio methacrylatis copolymerum B

Capsule
- gelatina
- titanii dioxidum E 171
- ferrum oxydatum rubrum E 172
- ferrum oxydatum flavum E 172

**Pharmaceutical form and active substance quantity per unit**

Modified-Release Capsule. Each capsule contains 30 mg propiverine hydrochloride.

**Indications/Uses**

Symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder.

**Dosage/Administration**

*Usual dosage*

The recommended daily doses are as follows:

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

*Dose adjustment/titration*

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.

*Patients with impaired hepatic function*

In patients with mildly impaired hepatic function, there is no need for a 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.

*Patients with impaired renal function*

In patients with mild or moderate impairment of renal function, no dose adjustment is required.

*Elderly patients*

Generally there is no special dose regimen for the elderly.

*Children and adolescents*

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

*Mode 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 propiverine.

Accordingly, there is no particular recommendation for the intake of propiverine in relation to food.

**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

**Warnings and precautions**

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 (classe 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.

Patients with galactose intolerance, total lactase deficiency or glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take this medicine.

**Interactions**

*Pharmacokinetic interactions*

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.

*Enzyme inhibitors*

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.

*Effect of Mictonorm modified-release capsules on other medicinal products*

- 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.

**Pregnancy, lactation**

*Pregnancy*

There are insufficient data from use in pregnant women.

Studies in animals have shown reproductive toxicity (more precise data under the heading "Preclinical data").

This medicin is not recommended during pregnancy.

*Lactation*

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.

**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.

**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 (≥1/1000 to <1/100)
Rare (≥1/10 000 to <1/1000)
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

*Description de certains effets indésirables*

During long-term therapy hepatic enzymes should be monitored, because reversible changes of liver enzymes might occur in rare cases.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

**Overdose**

*Signs and 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

**Properties/Effects**

*ATC code*

G04B D06

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.

*Pharmacodynamics*

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.
Clinical efficacy
Not relevant.

**Pharmacokinetics**

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.

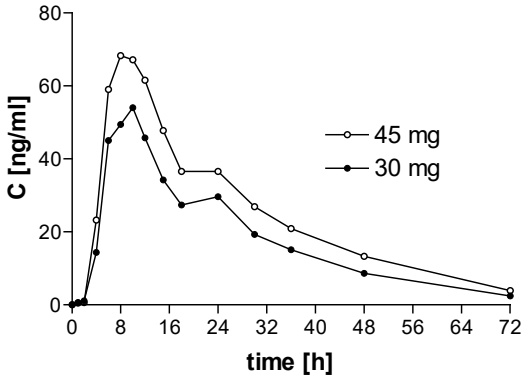
*Absorption*

After oral administration of Mictonorm , propiverine is absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 9,9 hours. The mean absolute bioavailability of Mictonorm is 60,8 ± 17,3% [arithmetic mean value ± SD for $ASC_{0-\infty}$ (per os) / $ASC_{0-\infty}$ (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 modified-release capsule leads to a peak plasma concentration ($C_{max}$) of about 70 ng/ml reached within 9,5 hours after administration. The $C_{max}$ values for the main metabolite propiverine-N-oxide were slightly increased by food (f = 1,26) whereas the extent of absorption was unchanged. Propiverine-N-oxide showed for all pharmacokinetic parameters 90 % confidence intervals within the acceptance ranges. An adjustment of dose in relation to food intake is not required.
Distribution
After administration of Mictonorm, steady state is reached after 4 to 5 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 and propiverine hydrochloride 45 mg modified-release capsules:*

| **Dose [mg]** | **30** | **45** |
|---|---|---|
| $ASC_{0-\infty}$ [ng·h/ml] | 1378<br>(903, 2104) | 1909<br>(1002, 3639) |
| $C_{max}$ [ng/ml] | 60,6<br>(41,5, 88,6) | 80,0<br>(41.8, 152.1) |
| $t_{1/2}$ [h] | 14,2<br>(10,8, 18,6) | 16,3<br>(13,9, 19,2) |
| $t_{max}$ [h] | 9,9<br>± 2,4 | 9,9<br>± 2,4 |

*Plasma concentrations of propiverine in 10 healthy volunteers after single dose administration of Mictonorm and propiverine hydrochloride 45 mg modified-release capsules:*

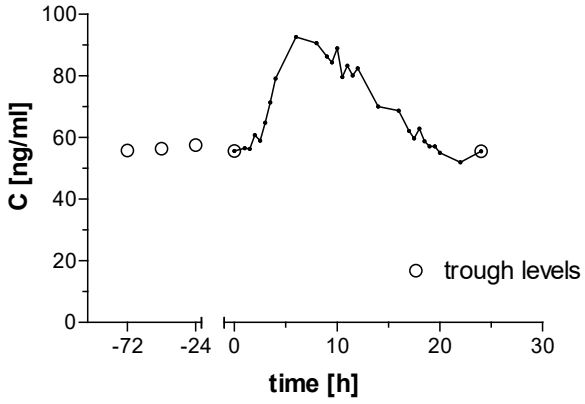



*Steady state characteristics of propiverine following multiple-dose administration to 24 healthy volunteers of propiverine hydrochloride 45 mg modified-release capsules once daily for 7 days:*

| | **geometric mean** | **range or ± SD** |
|---|---|---|
| ASC $_{0\text{-}24h}$ [ng/h/ml] | 1711 | 1079, 2713 |
| PTF* [%] | 109,4 | 81.2, 147,5 |
| $C_{average}$ [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 | ± 2,5 |

* PTF: peak-trough fluctuation

*Plasma concentrations of propiverine on day 7 and trough levels during treatment following multiple-dose administration of propiverine hydrochloride 45 mg modified-release capsules once daily for 7 days:*



*Metabolism*

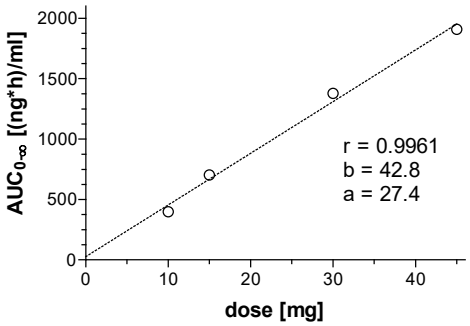
Propiverine is extensively metabolised by intestinal and hepatic enzymes. The primary metabolic route involves the oxidation of the piperidyl-N and is mediated by CYP 3A4 and flavin-containing monooxygenases (FMO) 1 and 3 and leads to the formation of the much less active N-oxide, the plasma concentration 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.

*Elimination*

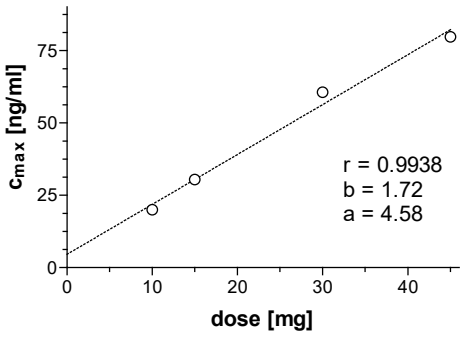
Following administration of 30 mg oral dose of $^{14}C$- propiverine hydrochloride to healthy volunteers, 60 % of radioactivity was recovered in urine and 21 % was recovered in faeces within 12 days. Less than 1 % of an oral dose is excreted unchanged in the urine. Mean total clearance after single dose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

Pharmacokinetic parameters of propiverine following oral administration of 10 – 45 mg of propiverine hydrochloride are linearly related to dose.

*Correlation between the oral dose of extended release propiverine and the resulting $AUC_{0-\infty}$:*




*Correlation between the oral dose of extended release propiverine and the resulting $C_{max}$:*




*Kinetics in specific patient groups*

*Hepatic impairment*

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.

*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.

*Elderly patients*

The comparison of trough plasma concentrations during steady state reveals no difference between older patients (60 tu 85 years, mean 68 years) and young healthy subjects. The ratio of parent drug to metabolite remains unchanged in older patients indicating the metabolic conversion of propiverine to its main metabolite, propiverine-N-oxide, not to be an age-related or limiting step in the overall excretion. As bioequivalence of propiverine hydrochloride 15 mg coated tablets administered 3 times a day and propiverine hydrochloride 45 mg coated tablets once a day was established in a good clinical practice compliant study the same can be concluded for Mictonorm 30 mg.

*Patients atteints d'un glaucome*

The treatment with Mictonorm will not lead to an increase of intraocular pressure in patients with open angle glaucoma and in patients with treated (controlled) angle closure glaucoma. This was shown in two placebo-controlled studies with propiverine hydrochloride 15 mg coated tablets administered 3 times a day for 7 days.

**Preclinical 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.

**Other information**

Incompatibilities
Not relevant.

*Shelf life*

The medicine should not be used after the date appearing after the word "EXP" on the package.

*Special precautions for storage*

Do not store above 30°C.
Store in the original package to protect from moisture.
Keep out of reach of children.

**Authorisation number**

67514 (Swissmedic)

**Packs**

Blisters of PVC/PVDC and aluminium foil in cartons of 7 and 28 capsules. (B).

**Marketing authorisation holder**

Labatec Pharma SA, 1217 Meyrin (Geneva)

**Date of revision of the text**

*Foreign comparator medicin: November 2017*
*Without addition of relevant safety information by Swissmedic: March 2020*