APONORM 15 MG COATED TABLETS

(Propiverine hydrochloride)

PL 15072/0008

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 11
Steps taken after authorisation – summary Page 12
Summary of Product Characteristics Page 13
Product Information Leaflet Page 20
Labelling Page 25
APONORM 15 MG COATED TABLETS

PL 15072/0008

LAY SUMMARY

The MHRA granted APOGEPHA Arzneimittel GmbH a Marketing Authorisation (licence) for the medicinal product Aponorm 15 mg Coated Tablets on 25 January 2011. This product is available as a prescription-only medicine (POM) for the treatment of people who have difficulty in controlling their bladders due to bladder overactivity or, in some cases, problems with the spinal cord.

Aponorm 15 mg Coated Tablets contain propiverine hydrochloride which prevents the bladder from contracting and increases the amount of urine that the bladder can hold. This medicine is used to treat the symptoms of overactive bladder.

No new or unexpected safety concerns arose from this simple application and it was, therefore, judged that the benefits of taking Aponorm 15 mg Coated Tablets outweigh the risks, hence a Marketing Authorisation has been granted.
APONORM 15 MG COATED TABLETS

PL 15072/0008

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Preclinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk benefit assessment Page 10
INTRODUCTION

The UK granted a Marketing Authorisation for the medicinal product Aponorm 15 mg Coated Tablets (PL 15072/0008) to APOGEPHA Arzneimittel GmbH on 25 January 2011. This product is available as a prescription-only medicine (POM) for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency that may occur in patients with overactive bladder syndrome or neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord injuries, e.g. transverse lesion paraplegia.

This product contains the active ingredient propiverine hydrochloride which exhibits anticholinergic and spasmolytic properties (ATC code G04B D06). Its mechanism of action is characterised by the modulation of intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis and the inhibition of the efferent connection of the nervus pelvis due to anticholinergic action.

The application was submitted as a simple abridged application according to Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC, cross-referring to Mictonorm 15 mg Coated Tablets (PL 15702/0002), which was approved on 23 April 1998 to the marketing authorisation holder APOGEPHA Arzneimittel GmbH.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product. As the cross-reference product was granted prior to the introduction of current legislation, no PAR was generated for it.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 15072/0008
PROPRIETARY NAME: Aponorm 15 mg Coated Tablets
ACTIVE(S): propiverine hydrochloride
COMPANY NAME: APOGEPHA Arzneimittel GmbH
LEGAL STATUS: POM

1. INTRODUCTION
This is a simple, piggyback application for Aponorm 15 mg Coated Tablets submitted under Article 10c (formerly Article 10.1(a)(i)) of Directive 2001/83/EC. The proposed MA holder is APOGEPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01309 Dresden, Germany.

The application cross-refers to Mictonorm 15 mg Coated Tablets (PL 15702/0002), approved on 23 April 1998 to the marketing authorisation holder APOGEPHA Arzneimittel GmbH.

The current application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed name of the product is Aponorm 15 mg Coated Tablets. The product has been named in-line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each coated tablet contains 15 mg propiverine hydrochloride equivalent to 13.64 mg propiverine. The product is stored polyvinylchloride/aluminium blister strips, which are inserted into a carton folder in pack sizes of 4, 20, 28, 30, 50, 56, 60, 100, 112, or 300 coated tablets.

The marketing authorisation holder (MAH) has stated they do not intend to market this product at the present time. However, the MAH has committed to submitting mock-ups of the packaging for any pack size to the relevant regulatory authorities for approval before marketing.

The proposed shelf-life (3 years) with the special storage conditions ‘Store in the original package.’ are consistent with the details registered for the cross-reference product.

2.3 Legal status
On approval, the product will be available as a prescription-only medicine (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
APOGEPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01309 Dresden, Germany.

The QP responsible for pharmacovigilance is stated.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in-line with the details registered for the cross-reference product.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10 TSE Compliance
With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. Confirmation has been provided from the supplier of lactose monohydrate that it is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms are used in the manufacture of the finished product. This is consistent with the cross-reference product.

3. EXPERT REPORTS
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL)/CARTON
PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference product.

The applicant has previously submitted results of PIL user testing for the reference product Mictonorm 15 mg Coated Tablets (PL 15702/0002). The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
As the leaflet for Mictonorm 15 mg Coated Tablets (PL 15702/0002) and these products are considered the same, no further user testing of the leaflets for this product is necessary.

Carton and blister
The proposed text complies with the relevant statutory requirements.

7. CONCLUSIONS
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.
PRECLINICAL ASSESSMENT

As this application is identical to the reference product Mictonorm 15 mg Coated Tablets (PL 15702/0002), no new preclinical data have been supplied with this application and none are required.

A preclinical expert report has been written by a suitably qualified person and is satisfactory.

The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

As this application is identical to the reference product Mictonorm 15 mg Coated Tablets (PL 15702/0002), no new clinical data have been supplied with this application and none are required.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for this application is consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data are submitted and none are required for an application of this type.

EFFICACY
This application is identical to the previously granted application for Mictonorm 15 mg Coated Tablets (PL 15702/0002).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the cross-reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with propiverine hydrochloride e is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 09/11/2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 01/08/2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on 16/03/2006 and 15/12/2006.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 01/09/2006 and 10/06/2010.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 24/01/2011.</td>
</tr>
</tbody>
</table>
APONORM 15 MG COATED TABLETS

PL 15072/0008

STEPS TAKEN AFTER ASSESSMENT

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT
Aponorm 15 mg Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each coated tablet contains 15 mg propiverine hydrochloride equivalent to 13.64 mg propiverine.

Each coated tablet contains 63 mg lactose monohydrate, 0.6 mg glucose monohydrate, 49 mg sucrose, and 0.15 mg Cochineal Red A (E 124).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Coated tablets
Rose-coloured, biconvex, round sugar-coated tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome or neurogenic detrusor overactivity (detrusor hyperreflexia) from spinal cord injuries, e.g. transverse lesion paraplegia.

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. Some patients may already respond to a dosage of 15 mg a day.
For neurogenic detrusor overactivity a dose of one coated tablet three times a day is recommended. The maximum recommended daily dose is 45 mg.

Elderly: Generally there is no special dosage regimen for the elderly (see 5.2).

Use in renal impairment
In patients with mild to moderate impaired renal function there is no need for a dose adjustment. 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 is 30 mg.

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.

A high fat meal increases the bioavailability of propiverine. Therefore, propiverine should be taken before a meal; especially in patients with renal or hepatic impairment (see 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 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 4.4, 4.5, 5.2).

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.

4.4 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 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.

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 4.2, 4.5, 5.2).

Patients with rare hereditary problems of galactose intolerance, the lapp lactose deficiency or glucose-galactose malabsorption should not take this medication.

Cochineal red A (E124, lake) may cause allergic reactions.

Due to a lack of data Aponorm 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 asazole antifungals (e.g. ketoconazole, itraconazole) or macrolide antibiotics (e.g. erythromycin, clarithromycin) have not been performed.
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 (see 4.2, 5.2).

4.6 Pregnancy and lactation
In animal studies, skeletal retardation in the offspring occurred when the drug was administered orally at high doses to pregnant females. The drug was also secreted into the milk of lactating mammals.

Propiverine hydrochloride should therefore not be administered to pregnant or 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
Within each system organ class, the undesirable effects are ranked under heading of frequency using the following convention:
Very common \(\geq 1/10\)
Common \(\geq 1/100 \text{ to } <1/10\)
Uncommon \(\geq 1/1,000 \text{ to } <1/100\)
Rare \(\geq 1/10,000 \text{ to } <1/1,000\)
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

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) 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 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. phystostigmine) 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 the 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 Aponorm 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 Aponorm 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 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.
**Distribution**

After administration of Aponorm 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 ($C_{\text{average}} = 61 \text{ ng/ml}$). 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 Aponorm 15 mg Coated Tablets (t.i.d. for 6 days):*

<table>
<thead>
<tr>
<th></th>
<th>single dose</th>
<th>multiple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>time [h]</td>
<td>0 8 16 24 32 40 48 56 64 72</td>
<td>0 4 8 12 16 20 24</td>
</tr>
<tr>
<td>[ng/ml]</td>
<td>40 30 20 10 0</td>
<td>80 60 40 20 0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose interval [h]</th>
<th>AUC$_{0-\infty}$ [ng.h/ml]</th>
<th>CV [%]</th>
<th>PTF [%]</th>
<th>$C_{\text{average}}$ [ng/ml]</th>
<th>CV [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 8</td>
<td>515</td>
<td>35</td>
<td>57</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>8 - 16</td>
<td>460</td>
<td>33</td>
<td>70</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>16 - 24</td>
<td>421</td>
<td>36</td>
<td>52</td>
<td>52</td>
<td>36</td>
</tr>
</tbody>
</table>

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-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; two of them are pharmacologically active and may contribute to the therapeutic efficacy of Aponorm 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 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). 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. Aponorm 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 (Aponorm 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 Aponorm 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 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Tablet core:
- Lactose monohydrate,
- powdered cellulose,
- magnesium stearate,

Tablet coat
- sucrose
- talc
- heavy kaolin
- calcium carbonate
- titanium dioxide (E171)
- acacia gum
- colloidal anhydrous silica
- Macrogol 6000
- glucose monohydrate
- Cochineal red A (E124, lake)
- montan wax.
6.2 **Incompatibilities**  
Not applicable

6.3 **Shelf life**  
3 years

6.4 **Special precautions for storage**  
Store in the original package

6.5 **Nature and contents of container**  
PVC/aluminium blisters are available in cartons of 14, 20, 28, 30, 50, 56, 60, 100, 112, or 300 coated tablets.  
Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**  
No special requirements

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

8 **MARKETING AUTHORISATION NUMBER(S)**  
PL 15072/0008

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
25/01/2011

10 **DATE OF REVISION OF THE TEXT**  
25/01/2011
PACKAGE LEAFLET: INFORMATION FOR THE USER

Aponorm® 15 mg Coated Tablets
(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 Aponorm 15 mg Coated Tablets (referred to as Aponorm 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 Aponorm is and what it is used for
2. Before you take Aponorm
3. How to take Aponorm
4. Possible side effects
5. How to store Aponorm
6. Further information

1. WHAT AAPONORM IS AND WHAT IT IS USED FOR

Aponorm is used for the treatment of people who have difficulty in controlling their bladders due to bladder overactivity or, in some cases, problems with the spinal cord. Aponorm contains the active substance propiverine hydrochloride. This substance prevents the bladder from contracting and increases the amount that the bladder can hold. Aponorm is used to treat the symptoms of overactive bladder.

2. BEFORE YOU TAKE AAPONORM

Do not take Aponorm
- if you are allergic (hypersensitive) to propiverine hydrochloride or to any of the other ingredients of the Aponorm (these are listed in section 6, Further information)
- 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)
  - intestinal atony
  - severe ulcerative colitis (inflammation of the bowel)
  - 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 (tachyarrhythmias)
Take special care with Aponorm

Before you take Aponorm you should tell your doctor if you have:
- autonomic neuropathy (paralysis of parts of the nervous system)
- severe kidney problems
- moderate or severe liver problems
- severe heart failure
- enlargement of the prostate gland (prostatic hypertrophy)
- heartburn and indigestion due to back flow of gastric juice into the throat (hiatus hernia with reflux oesophagitis)
- irregular heart beat (cardiac arrhythmia)
- fast heart beat (tachycardia)

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 your Aponorm:
- antidepressants (e.g. imipramine, sertraline, paroxetine),
- sedatives (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)
- neuroleptics such as phenothiazines, olanzapine, quetiapine (drugs usually used to treat hay fever, nausea and vomiting, difficulty in sleeping, anxiety),
- beta stimulants (drugs used to treat asthma, heart conditions, eye problems, blocked nose),
- isoniazide (a treatment for tuberculosis) and
- metoclopramide (used to treat nausea and vomiting)

Nevertheless, it may still be all right for you to take Aponorm. 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 Aponorm with food and drink

The coated tablets should be swallowed whole before meals.

Pregnancy and breast-feeding

If you are pregnant, likely to become pregnant or are breast-feeding you should not take Aponorm.

Driving and using machines

Aponorm 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 X
Aponorm contains glucose, lactose, and sucrose (sugars). 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 AПОНОРМ

Always take Aponorm 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 coated tablets you should take and when. Take your coated tablets at the same time each day.

Adults and the elderly: The usual dose of Aponorm is two or three coated tablets daily.

Aponorm is not recommended for children.

If you take more Aponorm 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 coated tablets with you.

If you forget to take Aponorm

Do not worry. Take your recommended dose as soon as you remember, unless it is nearly time for the next dose. Then take your next dose at the right time. Do not take a double dose to make up for a missed dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Aponorm can cause side effects although not everybody gets them.

The following side effects have also been reported:

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

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

Uncommon side effects (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 side effects (affects 1 to 10 users in 10,000)
- rash

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

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.

All medicines can cause allergic reactions although serious allergic reactions are very rare. If you get any of the following symptoms during treatment, you should contact your doctor immediately:
- 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.

In theory, 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.

5. HOW TO STORE AПОNORM

Keep Aponorm out of the reach and sight of children.
Store in the original package to protect the coated tablets from light and moisture.

Do not use Aponorm after the expiry date, which is stated on the carton after EXP. The expiry date refers to the last

6. FURTHER INFORMATION

What Aponorm contains:
The active substance is propiverine hydrochloride. Each coated tablet contains 15 mg of propiverine hydrochloride

The other ingredients are lactose monohydrate; powdered cellulose; magnesium stearate; sucrose; talcum; heavy kaolin; calcium carbonate; titanium dioxide (E171); acacia gum; colloidal anhydrous silica; Macrogol 6000; glucose monohydrate; Cochineal red A (E124, lake); Montan wax.

What Aponorm looks like and the contents of the pack:
Aponorm 15mg Coated Tablets are rose-colored sugar coated tablets.
PVC/aluminium blisters in cartons of 14, 20, 28, 30, 50, 56, 60, 100, 112, or 300 coated tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
APOGEPHA Arzneimittel GmbH
Kyffhäuserstraße 27
01309 Dresden
Germany

This leaflet was last approved in XXX.
LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Aponorm 15 mg Coated tablets
Propiverine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified release capsule contains 15 mg propiverine hydrochloride (equivalent to 13.64 mg propiverine).

3. LIST OF EXCIPIENTS

Also includes: Glucose monohydrate, lactose monohydrate, sucrose, cochineal red A (E 124, lake) and other ingredients

4. PHARMACEUTICAL FORM AND CONTENTS

14 coated tablets
20 coated tablets
28 coated tablets
30 coated tablets
50 coated tablets
56 coated tablets
60 coated tablets
100 coated tablets
112 coated tablets
300 coated tablets

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:

9. SPECIAL STORAGE CONDITIONS

No special precautions for storage. Store in the original package.

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

APOGPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01309 Dresden, Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 15072/0008

13. BATCH NUMBER

< To be completed nationally >

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Do not crush or chew.

16. INFORMATION IN BRAILLE

APONORM 15 MG COATED TABLETS
### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### ALUMINIUM/PVC BLISTERS

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aponorm 15 mg coated tablets</td>
</tr>
<tr>
<td>Propiverine hydrochloride</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. NAME OF THE MARKETING AUTHORISATION HOLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOGEPHA Arzneimittel GmbH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiry date:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch number:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. OTHER</th>
</tr>
</thead>
</table>