Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Aponorm XL 45 mg modified release capsules

(propiverine hydrochloride)

Procedure No: UK/H/6862/001/DC

UK Licence No: PL 15072/0018

APOGEPHA Arzneimittel GmbH

LAY SUMMARY

Aponorm XL 45 mg modified release capsules (propiverine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Aponorm XL 45 mg modified release capsules (PL 15072/0018; UK/H/6862/001/DC). For ease of reading, the product will be referred to as 'Aponorm XL 45 mg' in this lay summary. The lay summary explains how the application for Aponorm XL 45 mg was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Aponorm XL 45 mg.

For practical information about using Aponorm XL 45 mg, patients should read the package leaflet or contact their doctor or pharmacist.

What is Aponorm XL 45 mg and what is it used for?

Aponorm XL 45 mg is a medicine which is used for the treatment of people who have difficulty in controlling their bladder due to bladder overactivity It is a modified release capsule that needs only to be taken once a day.

How does Aponorm XL 45 mg work?

Aponorm XL 45 mg contains the active substance propiverine hydrochloride. This substance prevents the bladder from contracting and increases the amount that the bladder can hold. In this way, Aponorm XL 45 mg treats the symptoms of overactive bladder.

How is Aponorm XL 45 mg used?

Aponorm XL 45 mg is available as a modified release hard capsule and is taken by mouth.

This medicine should be taken exactly as instructed by the patient's doctor. The patient should check with his/her doctor if they are not sure.

<u>The recommended dose is:</u>
Adults and the elderly: The usual dose of Aponorm XL 45 mg is one capsule daily.
Use in children and adolescents: Aponorm XL 45 mg is not recommended for children.

<u>Method of Administration</u>
The capsule(s) should be swallowed whole with a drink of water. The patient should not crush or chew the capsules. Aponorm XL 45 mg may be taken with or without food.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.This medicine can only be obtained with a prescription.

What benefits of Aponorm XL 45 mg have been shown in studies?

The company, provided its own data on pharmacology, efficacy and safety studies of the active substance propiverine hydrochloride. In addition, data has been provided from the published literature on propiverine. These studies have shown that Aponorm XL 45 mg is effective in the proposed indication.

What are the possible side effects of Aponorm XL 45 mg?

Like all medicines, Aponorm XL 45 mg can cause side effects although not everybody gets them.

Very common (may affect more than 1 in 10 people)
- dry mouth

Common (may affect up to 1 in 10 people)
- abnormal vision and difficulty in focussing
- fatigue
- headache
- abdominal pain
- indigestion
- constipation

For the full list of all side effects reported with Aponorm XL 45 mg see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Aponorm XL 45 mg.

Why is Aponorm XL 45 mg approved?
It was concluded that, in accordance with EU requirements that, for Aponorm XL 45 mg, its benefits are greater than the risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Aponorm XL 45 mg?
A Risk Management Plan (RMP) has been developed to ensure that Aponorm XL 45 mg is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Aponorm XL 45 mg, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects will be continuously monitored in the post-marketing setting. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Aponorm XL 45 mg
Spain and the UK agreed to grant a Marketing Authorisation for Aponorm XL 45 mg on 08 August 2018. A Marketing Authorisation for Aponorm XL 45 mg was granted in the UK to APOGEPHA Arzneimittel GmbH on 06 September 2018.

The full PAR for Aponorm XL 45 mg follows this summary.

For more information about treatment with Aponorm XL 45 mg, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

SCIENTIFIC DISCUSSION

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Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Spain considered that the application for Aponorm XL 45 mg modified release capsules (PL 15072/0018; UK/H/6862/001/DC) could be approved. For ease of reading, the product may be referred to as 'Aponorm XL 45 mg' in this scientific discussion.

Aponorm XL 45 mg is a Prescription Only Medicine (POM), which is indicated in adults for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder.

The active substance, propiverine hydrochloride, is detrusor relaxant drug with anticholinergic and calcium-modulating properties.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Spain as Concerned Member State (CMS). The application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, for a new product with a known active substance (mixed dossier). The application for Aponorm XL 45 mg is submitted as a mixed dossier, which contains updated documentation in terms of clinical information.

Propiverine was first approved in Germany in 1981 as a 15 mg immediate release (IR) formulation to be administered two or three times daily in adults with overactive bladder (OAB). The IR formulation was approved in the UK 1998.

The modified release (MR) formulation under consideration was developed as a line extension to propiverine IR 15 mg twice daily (b.i.d.) and to the 30 mg MR formulation Aponorm XL 30 mg modified-release capsules (PL 15072/0017), which was approved on 03 February 2017 through a decentralised procedure (UK/H/6097/001/DC), under Article 8(3) of Directive 2001/83/EC, as amended.

The proposed product is also essentially the same as the applicant's product, Mictonorm XL 45 mg Modified Release Capsules (PL 15072/0010; UK/H/4594/001/MR), which was first approved in the UK on 30 November 2009.

No new non-clinical studies were conducted, which is acceptable given that the application is for a new product containing a known active substance.

The clinical dossier supporting this application consists of the results of clinical studies submitted with the previously approved immediate release 15 mg formulation and modified release 30 mg formulation and additionally new clinical studies with propiverine at a daily dose of 45 mg that evaluated efficacy and safety. The clinical studies are stated to have been conducted in accordance with Good Clinical Practice (GCP) principles.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The UK and Spain considered that the application could be approved at the end of procedure (Day 204) on 08 August 2018. After a subsequent national phase, a Marketing Authorisation was granted in the UK to APOGEPHA Arzneimittel GmbH on 06 September 2018.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is an orange, modified release hard capsule (size 2) containing white to off-white pellets.

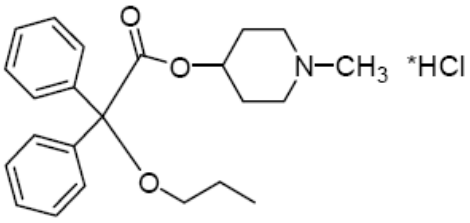
Each capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).The product also contains pharmaceutical excipients in the capsule pellet and capsule shell, namely citric acid, povidone, lactose monohydrate, talc, triethyl citrate, magnesium stearate, methacrylic acid–methyl methacrylate copolymer (1:1), methacrylic acid-methyl methacrylate copolymer (1:2), ammonio methacrylate copolymer type A, ammonio methacrylate copolymer type B, gelatin, titanium dioxide E171, red iron oxide E172 and yellow iron oxide E172. Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polyvinylchloride/polyvinylidene chloride (PVC/PVDC) and aluminium blisters in cartons of 7, 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112 and 280 hard capsules. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Propiverine hydrochloride

INN:	Propiverine hydrochloride
Chemical Name:	2,2-diphenyl-2-(1-propoxy)acetic acid-(1-methylpiperid-4-yl)ester hydrochloride
Molecular Formula:	$C_{23}H_{30}ClNO_3$
Structure	
M_r:	403.95
Appearance:	A white, crystalline, water-soluble powder of bitter, burning taste.
Solubility	Soluble in water
Chirality:	Propiverine hydrochloride does not exhibit optical isomerism
Polymorphism	Propiverine hydrochloride does not exhibit polymorphism.

Propiverine hydrochloride is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential and known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging. The primary packaging has been shown to comply with current guidelines concerning contact with food.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable modified release hard capsule formulation containing 45 mg of propiverine, as the active ingredient. The development was based on the rationale that there is a relationship between the pharmacological/toxicological response and the systemic exposure to the drug/metabolites. The aim of the development was to reach a similar total exposure to the drug as for the IR formulation. A satisfactory account of the pharmaceutical development has been provided.

With the exception of red iron oxide E172 and yellow iron oxide E172 which are controlled to their respective United States Pharmacopoeia (USP) monograph/National Formulary (NF) specifications, all the excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate and gelatin, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data that comply with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 4 years, with the special temperature storage conditions, 'Do not store above 30°C'. and 'Store in the original package to protect from moisture' has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Aponorm XL 45 mg, from a quality point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of propiverine hydrochloride are well known. No new non-clinical data have been submitted for this application and none are required.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

The pharmacology of the active substance, propiverine hydrochloride, is adequately discussed in the Marketing Authorisation Holder's (MAH's) non-clinical overview and is briefly summarised below.

In *in vitro* studies with detrusor muscle strips from mice, guinea pigs and pigs, propiverine exhibited an antimuscarinic mode of action which was less pronounced than that of atropine. *In vivo* studies in rats and mini pigs showed that propiverine caused an increase in bladder capacity and lowered micturition pressure.

At high doses administered to rats, propiverine exhibited a dopamine agonistic effect.

In safety pharmacology studies effects were consistent with that of anticholinergic action. Propiverine enhanced spontaneous motor activity and prolonged hexobarbital sleeping time. In guinea pig papillary muscles and canine Purkinje fibres, propiverine shortened the action potential duration suggestive of inhibition of L-type Ca^{2+} current. In transfected HEK-293 cells propiverine showed a concentration dependent inhibition of hERG current. In rats and dogs, propiverine caused an increase in blood pressure and heart rate. The adverse effects in cardiac parameters in non-clinical studies are not a cause for concern as there is an acceptable safety margin to clinical doses. In addition, anti-cholinergic effects - tachycardia (cardiovascular), angle closure glaucoma (eye) and faecaloma, subileus (gastrointestinal) are highlighted in the applicant's Risk Management Plan as important identified/potential risks.

III.3 Pharmacokinetics

The pharmacokinetics of the active substance, propiverine hydrochloride is adequately discussed in the MAH's non-clinical overview and are briefly summarised below.

In rats administered propiverine orally, blood concentrations increased rapidly, were maintained at a sustained high level up to 12 h and decreased thereafter with elimination half-lives of 13.5 h (male rats) and 10.4 h (female rats). After intravenous administration, blood concentrations showed biexponential elimination. The volume of distribution was 12.1 L/kg. The amount absorbed of propiverine after oral

administration was about 80% on the basis of the AUC ratio after oral and intravenous administration.

Rats were administered propiverine at 1, 10, or 100 mg/kg by gavage or 10 mg/kg IV, Beagle dogs were given 10 mg/kg by gavage and IV, and male Rhesus monkeys were given 10 mg/kg by gavage. After oral administration of 1 mg/kg in rats, propiverine was only measurable at 0.5 and 1 h.. Values for C_{max} appeared to be dose-related between 10 mg/kg and 100 mg/kg. In rats, there was a nonlinear increase of the AUC values of the parent drug and of all metabolites measured after oral single doses of 10 vs 100 mg/kg, the 10-fold higher dose results in an increase of the AUCs of P4 and P4NO by 24-fold and 64-fold, respectively.

There was a considerable difference between oral and intravenous AUC_{0-72h} in the rat following a dose of 10 mg/kg. The oral bioavailability was calculated as approximately 2%. A first pass effect by the liver and other tissues seems to play an important role with respect to the extent of systemic exposure towards the parent compound in this species. Oral bioavailability was higher in the dog. About 49% was obtained by comparing AUC values after intravenous and oral administration. As far as elimination half-life has been calculated, there was no striking difference between rats, dogs and monkeys. Values ranged between 3 - 5 h. T_{max} was rather similar in rats and dogs (about 2 h) but greater in monkeys (about 5.5 h).

At 1 hour after oral dosing in male rats, the liver, urinary bladder, lung, kidney, hypophysis, prostate, adrenal gland, pancreas, mesenteric lymph node, spleen, thyroid, submaxillary gland, bone marrow, heart and parotid gland showed concentrations higher than the plasma level. The concentration in other tissues and organs was lower than the plasma level. The concentrations in the liver, urinary bladder, lung and kidney were more than 5-fold higher than the plasma radioactivity. At 8 hours post-dose, plasma concentration was not changed significantly, whereas most of the tissues and organs attained levels of radioactivity higher than the plasma level except for the brain, eye ball and sciatic nerve. The lung, liver, kidney, urinary bladder, pancreas, hypophysis, and adrenal gland showed concentrations 5-fold higher than the plasma concentration. In contrast, the radioactivity in the brain and eye ball was only 0.26-fold and 0.51-fold the plasma concentration, respectively. At 24 h and thereafter, the concentrations of radioactivity in most of the tissues decreased along with the elimination of plasma radioactivity. The liver, kidney, and skin showed a slightly retarded elimination. The delay of elimination was most pronounced in the liver. The concentration in the stomach reached the maximum level at 1 h after dosing and decreased thereafter. Tissue concentrations in the small intestine and those in the caecum and colon reached maximum levels at 8h and 24 h, respectively, and decreased thereafter. At 48 and 72 h after dosing, radioactivity was mostly eliminated from the gastrointestinal contents to amounts not more than 1% of the administered dose in either part of the gastrointestinal tract. The plasma concentrations in female rats after oral dosing were slightly lower than those in the male rats, whereas the tissue concentrations were slightly higher.

^{14}C-labelled propiverine 100 mg/kg was administered orally, to pregnant rats on day 11 and day 18 of pregnancy and 12 days after parturition. The amounts of radioactivity crossing the placenta were relatively low resulting in concentrations in the foetus about 2-fold the maternal plasma level at peak time. The elimination of radioactivity from the foetus was very rapid. The uptake of radioactivity into foetal tissues was slightly higher during the later period of gestation. The ratio of radioactivity in the foetal liver compared to that in the total foetus was relatively low at day 18 of gestation. The hepatic uptake in the foetus was not marked in comparison to the mother animals. In the whole-body autoradiography of the foetuses, no extensive localization of radioactivity in the foetal liver was observed either.

After administration of ^{14}C-labelled propiverine to lactating rats, the concentrations in the milk were about 1.2- 1.7-fold higher than the corresponding plasma levels at any time point investigated. The elimination half-life of the milk radioactivity was about 13 hours.

Liver, kidney, lung and small intestine homogenates from rats, dogs and monkeys were incubated with ^{14}C-propiverine. In rat liver homogenates, propiverine concentrations showed a rapid decrease. The major metabolites formed were P4NO, P0NO, M-14, and M-4. The rate of metabolism of propiverine was

131 nM/min/g tissue and rates of formation of P4NO and M-14 were 78 and 32 nM/g tissue, respectively. In the dog, P4NO and M-14 were detected as major metabolites. The rate of metabolism of propiverine was slower than in the rat. The rate of metabolism of propiverine and the rates of formation of P4NO and M-14 were 12.8, 6.7 and 4.5 nM/min/g tissue, respectively. The monkey liver showed a rate of metabolism between those in the liver homogenates of rats and dogs. The rate of metabolism of propiverine and the rates of formation of P4NO and M-14 were 50.3, 32.3 and 10.7 nM/min/g tissue, respectively. In the rat kidney homogenates, propiverine was metabolized slowly and formation of P4NO and a small amount of M-14 were found. Propiverine was virtually not metabolized by the dog and monkey kidney. In the rat and the dog lung homogenates, propiverine was slowly metabolized to P4NO. No metabolism of propiverine was observed in the lung homogenates of monkeys.

Rats were administered 100 mg/kg ^{14}C-labelled propiverine. Non-radioactive propiverine was orally given at a dose of 300 mg/kg. Nine metabolites of propiverine were found in urine and bile (P4NO, P0NO, M-2, M-14, M-4, M-1, M-7, M-8, and M-9). The portal plasma concentration of the parent compound was 4 – 16-fold higher than in peripheral plasma. This is compatible with a hepatic first pass metabolism. In plasma, the same metabolites as found in urine and bile were detected, with the exception of M-14 and M-1. Major metabolites were M-2 (~21% of total sample content), M-7 (15.6%), and M-9 (~10%). Following oral administration, P0NO was the major metabolite detected in urine (~44%), whereas M-9, M-7, M-1 were the major metabolites found in the bile (~5 - 8%). Glucuronide and sulphate conjugates, accounting for only 3- 4% of the administered dose, were detected in urine and bile. About 19% of plasma activity, 31.5% of urine activity and 56% of bile activity were of unknown origin. It cannot be totally excluded that M-7 is an analytical artefact derived from M-23.

In Beagle dogs administered 10 mg/kg IV or orally, the major metabolites identified in urine were M-1, P0NO, M-7, M-9 and M-2. The major urinary metabolite in the dog is M-1 irrespective of the route of administration. However, it cannot be totally excluded that M-1 is an analytical artefact derived from M-23. Depending on the route of administration there are differences in the amount excreted into urine for P0NO and M-2. P0NO is generated by an intensive first pass metabolism.

Major metabolites identified in monkeys following 10 mg/kg given orally were P0NO, M-1, M-7 and M-9.

In rats administered a single dose^{14}C-labelled propiverine, males excreted about 40% and 55% of the administered radioactivity in urine and faeces, respectively. Female animals excreted about 33% and 70% of the administered radioactivity in urine and faeces, respectively, during a period up to 72 hours. Most of the radioactivity was recovered in the excreta during the period up to 48 h after drug supply. The residual radioactivity in the carcass at 72 h after administration was very low (about 0.6%) in male and female rats. There was no accumulation of radioactivity. Following intravenous administration, about 22% and 73% of the dose were excreted in urine and faeces, respectively. The residual radioactivity in the carcass at 72 h after intravenous administration was very low (about 0.6%). The faecal excretion of 14C-labelled propiverine was very low.

III.4 Toxicology

The toxicology properties of propiverine hydrochloride are discussed in detail in the MAH's non-clinical overview. The summaries of these findings are presented below:

Acute toxicity studies reported in mice, rats, rabbits and dogs suggested the development of tremor, convulsions, dyspnoea, bradypnoea, and congestion of organs.

In rats and dogs, liver weights were increased after chronic exposure commensurate with induction of drug-metabolising enzymes. These findings were reversible or improved during recovery. Despite the low safety margin to clinically relevant doses, no dose-limiting hepatotoxicity has been found clinically.

Propiverine was negative for genotoxicity in in vitro and in vivo studies. The potential for carcinogenicity with propiverine seen in male mice and rats has been demonstrated as species-specific. There was no effect on fertility or reproductive ability, except at high oral doses.

The non-clinical overview does not provide a discussion of the impurity profile and excipients as recommended in the Notice to Applicants, Volume 2B. Data to assess this has however been reviewed from other sections of the dossier. The proposed excipients are well-known and are commonly-used in pharmaceutical products and therefore no safety concerns arise from their inclusion in the proposed product. The impurities associated with the drug substance and drug product appear to be well controlled and within the limits set out in ICH guidelines, therefore no toxicological qualification is necessary.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00 Corr 2], the Applicant submitted a full Environmental Risk Assessment (ERA) for propiverine hydrochloride.

Determined by Partition Coefficient OECD 117, propiverine shows a log n-octanol/water partition coefficient ($\log K_{ow}$) of 4.37, which is below the guidance lower limit value of 4.5. Therefore, propiverine is unlikely to be a persistent, bioaccumulative, toxic (PBT) substance.

In the Phase I assessment, the Predicted Environmental $\text{Concentration}_{SURFACEWATER}$ ($PEC_{sw)}$ value (0.225 µg/l) for propiverine, calculated using a maximum daily dose of propiverine consumed per inhabitant ($DOSE_{ai}$) of 45 mg and the default values for percentage of market penetration (F_{pen}), amount of wastewater per inhabitant per day ($WASTEW_{inhab}$) and dilution factor (DILUTION) results, was above the the action threshold (0.01 µg/L), so further testing and analysis was conducted (Phase II testing).

The outcome of the Phase II Tier A analysis:

1. The Predicted Environmental $\text{Concentration}_{SURFACEWATER}$/Predicted No-Effect $\text{Concentration}_{WATER}$ is below 1, therefore further testing in the aquatic compartment is not required.
2. The Predicted Environmental $\text{Concentration}_{GROUNDWATER}$ (PECsw)/Predicted No Effect $\text{Concentration}_{GROUNDWATER}$ is below 1; further evaluation is not required.
3. The n-octanol/water partition coefficient $\log K_{ow}$ is below 4.5, therefore the bioconcentration factor has no impact on Tier B.
4. The adsorption/desorption data indicates the affinity for drug substance to bind to sewage sludge below K_{OC} 10000 L/kg. Therefore, further environmental assessment of the drug substance in the terrestrial compartment is not required.

Phase II Tier B analysis:

In Phase II Tier, a bioconcentration study in Zebrafish (OECD 305) was conducted; the results of the study was satisfactory and raised no concerns.

The effects of propiverine hydrochloride on the environment have been fully characterised in line with according to the Guideline on the Environmental Risk Assessment of Medicinal Products of Human Use (EMEA/CHMP/SWP/4447/00). No further action regarding environmental fate is required.

III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Aponorm XL 45 mg, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of propiverine hydrochloride.

The Applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

To support the application, the Applicant has submitted the results of clinical studies with their previously approved 15 mg immediate release and 30 mg modified release formulations, as well as the current modified release 45 mg formulation.

IV.2 Pharmacokinetics

The pharmacokinetics (PK) of propiverine and its main metabolites after administration of immediate release propiverine is well established.

The pharmacokinetic programme is identical to that presented for approved Aponorm XL 30 mg modified release capsules (PL 15072/0017;UK/H/6097/001/DC). A short description of relevant PK studies conducted with the modified release formulation is described below.

Study 1
An open prospective crossover bioavailability study of absorption in the small intestine

The absorption of propiverine from different sites of the small intestine was examined in an open cross-over study. Dissolved propiverine hydrochloride (15 mg) was given to 4 healthy male subjects via intestinal tubing into different parts of the small intestine (a proximal and a considerably more distal site). The appearance of propiverine in the circulation was followed by serum concentration measurements of propiverine and its main metabolite M-5. Blood samples were drawn up to 480 minutes after drug administration. The bioavailability of propiverine was not different between the lower part of the small intestine compared to the upper small bowel. There was a greater AUC of the metabolite M-5 after proximal intestinal administration compared to the more distal administration.

Study 2
A single-dose, double blind, randomised, five treatment period, crossover study to assess the dose proportionality and absolute bioavailability of the modified release formulation of propiverine hydrochloride in healthy volunteers

Volunteers were given one the following treatments in each treatment period:

1 capsule of 10mg modified release formulation
1 capsule of 15mg modified release formulation
1 capsule of 30mg modified release formulation
1 capsule of 45mg modified release formulation
5ml intravenous solution of propiverine (3mg/ml)

Blood samples were taken 96 hours after oral administration and 72 hours after intravenous administration. There was a washout period of at least 7 days between the treatment periods.

A summary of the results is shown in the table below:

Parameter	ER 10 mg	ER 15 mg	ER 30 mg	ER 45 mg	15 mg i.v.
$AUC_{0-\infty}$ [(ng*h)/mL]	398 (160, 995)	702 (465, 1059)	1378 (903, 2104)	1909 (1002, 3639)	1178 (825, 1682)
C_{max} [ng/mL]	20.0 (12.4, 32.1)	30.0 (23.6, 39.1)	61.0 (41.5, 88.6)	80.0 (41.8, 152.1)	--
$t_{1/2}$ [h]	12.5 (6.9, 32.1)	14.2 (10.3, 19.5)	14.2 (10.8, 18.6)	16.3 (13.9, 19.2)	12.9 (7.5, 22.3)
t_{max} [h]	10.4 ± 5.3	9.6 ± 1.8	9.9 ± 2.4	9.9 ± 2.4	--
F [%]	61.0 ± 27.0	61.5 ± 16.5	60.8 ± 17.3	59.5 ± 23.3	--
CL_{tot} [mL/min]	418 (168, 1044)	356 (236, 537)	363 (238, 554)	393 (206, 749)	212 (149, 303)

geometric means (ln SD) or arithmetic means ± SD, as appropriate

The results showed that there appeared to be a dose proportional increase in linearity with increasing doses of the modified release formulation of propiverine. Dose-linearity was observed from 10 mg to 45 mg of propiverine in terms of the rate and extent of exposure.

The modified release formulation has been demonstrated to be bioequivalent to the immediate release formulation given thrice daily in terms of the extent of absorption and exploratory analysis suggest that the fluctuations of the steady state concentrations during once daily administration of the modified release formulation given once daily were not larger than those observed after administration of the immediate release formulation given thrice daily.

Study 3 (P 426)
In a randomised, open, 3- period, cross-over, single centre study, PK parameters of propiverine and its main metabolite M-5 after oral administration of modified release formulations were assessed in comparison to an immediate release formulation.

Propiverine was administered as a single oral dose to 6 healthy male volunteers at the following dosages:

Formulation P1 (22.5 mg) immediate release
Formulation P2 (45 mg) modified release
Formulation P3 (45 mg) modified release

The results are summarised in the table below:

Table : Comparison of bioavailability parameters for propiverine and M-5

Parameter	Formulation	Propiverine Point estimator (95% CI)	M-5 Point estimator (95% CI)
AUC_{0-t}	P2 / P1	1.06 (0.79 - 1.42)	0.68 (0.52 - 0.90)
	P3 / P1	1.05 (0.72 - 1.53)	0.61 (0.47 - 0.78)
$AUC_{0-\infty}$	P2 / P1	1.15 (0.73 - 1.80)	0.77 (0.55 - 1.07)
	P3 / P1	1.39 (0.79 - 2.42)	0.76 (0.58 - 0.98)
C_{max}	P2 / P1	0.49 (0.37 - 0.65)	0.30 (0.23 - 0.40)
	P3 / P1	0.37 (0.27 - 0.51)	0.19 (0.17 - 0.22)

Compared to the results of the immediate release formulation, P1 (considered as reference after dose correction) the modified release formulations P2 and P3 revealed no differences in the bioavailability of the parent drug. The amount of M-5 was significantly reduced after administration of P2 and P3 compared to P1. In agreement with the modified release characteristics of P2 and P3, the rate of absorption of propiverine was significantly reduced with lower C_{max} values compared to the results of formulation P1.

Study 4
This controlled, randomised, double-blind, double dummy, 2-period, crossover, bioequivalence study in 24 healthy volunteers was conducted to compare the equivalence of 15 mg three times daily of immediate release formulation (Mictonorm) with a 45 mg once daily of modified release formulation (it is considered pivotal for the 45 mg XL). Treatment was given for 7 days; there was a washout period of 14 days between treatments.

Propiverine (P4) and its major N-oxidised metabolite P4NO in serum and urine were analysed.

The results of the bioequivalence assessment of the primary and the main secondary criteria of Test vs Reference are listed in the table below.

Table: Bioequivalence assessment and pharmacokinetic results for propiverine

Parameter	Test Geometric Mean	Reference Geometric Mean	Test/Reference Point estimate (90% CI)
AUC_{0-24h} [ng.h/mL]	1711	1677	1.02 (0.87, 1.19)
PTF [%]	109.4	118.4	0.92 (0.82, 1.05)
C_{av} [ng/mL]	71	70	1.02 (0.87, 1.19)
C_{max} [ng/mL]	105	113	0.93 (0.80, 1.08)
C_{min} [ng/mL]	29	31	0.93 (0.82, 1.05)
$t_{1/2}$ [h]	20.4	14.4	1.41 (1.20, 1.66)
A_e (0-24h) [µg]	36.0	26.5	1.11 (0.79, 1.56)
CL_R [mL/min]	0.4	0.3	0.95 (0.56, 1.58)
CL_M [mL/min]	10.9	13.8	0.80 (0.66, 0.96)
t_{max} [h]	7.3	4.7	2.60 (1.19, 4.02)

This study showed that the two treatments are equivalent in terms of the extent of absorption.
More detailed exploratory analysis suggested that the fluctuations of the steady state concentrations during once daily administration of the modified release formulation given once daily were not larger than those observed after administration of the immediate release formulation given thrice daily.

Study 5
One food effect study was conducted to assess the effect of food on the pharmacokinetics of propiverine.

A randomised open four-way crossover food interaction study of propiverine modified release and immediate release in 24 healthy subjects

The subjects received the following medications in a randomised sequence:
- a single oral dose of two coated tablets Mictonorm (immediate release formulation) containing 15 mg propiverine hydrochloride each, after a high fat content meal
- a single oral dose of two coated tablets Mictonorm (immediate release formulation) containing 15 mg propiverine hydrochloride each, under fasting conditions

- a single oral dose of a capsule (modified release formulation) containing 45 mg propiverine hydrochloride, after a high fat content meal
- a single oral dose of a capsule (modified release formulation) containing 45 mg propiverine hydrochloride, fasting.

Results

Mean propiverine pharmacokinetic parameters- immediate release formulation

arithmetic mean ± SD / geometric mean		fasted	after meal	ratio	90%confidence interval
Cmax	(ng/mL)	80.5 ± 28.0 / 76.1	97.8 ± 27.1 / 94.32	1.239	1.11 – 1.39
tmax	(h)	2.17 ± 0.92 / 1.99	2.44 ± 1.44 / 2.15		
AUC(0-t)	(ng*h/mL)	764 ± 516 / 638	930 ± 402 / 849	1.331	1.13 – 1.57
AUC(0-T)	(ng*h/mL)	333 ± 110 / 317	383 ± 96 / 371	1.169	1.07 – 1.28
AUC(0-∞)	(ng*h/mL)	1178 ± 843 / 971	1483 ± 707 / 1312	1.351	1.13 – 1.61
t1/2	(h)	13.9 ± 11.3 / 10.4	17.3 ± 11.0 / 13.5		

Mean propiverine-N-oxide pharmacokinetic parameters -immediate release formulation

Mean Propiverine-N-oxide PK parameters (N=24) of the immediate release formulation					
arithmetic mean ± SD / geometric mean		fasted	after meal	ratio	90%confidence interval
Cmax	(ng/mL)	973 ± 214 / 952	735 ± 118 / 726	0.763	0.710 – 0.820
tmax	(h)	1.65 ± 0.94 / 1.46	2.58 ± 1.01 //2.37		
AUC(0-t)	(ng*h/mL)	9091 ± 2831 / 8696	8542 ± 2506 / 8211	0.944	0.890 – 1.002
AUC(0-T)	(ng*h/mL)	7822 ± 1780 / 7631	7087 ± 1538 / 6933	0.908	0.864 – 0.955
AUC(0-∞)	(ng*h/mL)	9669 ± 3150 / 9209	9120 ± 2595 / 8783	0.954	0.894 – 1.017
t1/2	(h)	13.5 ± 7.27 / 11.8	14.2 ± 5.89 / 13.11		

Mean propiverine pharmacokinetic parameters - modified release formulation

arithmetic mean ± SD / geometric mean		fasted	after meal	ratio	90%confidence interval
Cmax	(ng/mL)	70.2 ± 27.0 / 65.8	65.8 ± 16.5 / 63.9	0.971	0.877 – 1.075
tmax	(h)	9.54 ± 3.64 / 9.41	9.50 ± 1.35 / 9.41		
AUC(0-t)	(ng*h/mL)	1749 ±105 / 1522	1602 ± 548 / 1522	0.999	0.885 – 1.238
AUC(0-T)	(ng*h/mL)	614.2 ± 231 / 580	572 ± 146 / 555	0.957	0.879 – 1.042
AUC(0-∞)	(ng*h/mL)	2422 ± 1181 / 2218	2333 ± 814 / 2212	0.997	0.893 – 1.113
t1/2	(h)	23.4 ± 12.7 / 20.7	24.1 ± 11.5 / 22.2		

Mean propiverine-N-oxide pharmacokinetic parameters- modified release formulation

arithmetic mean ± SD / geometric mean		fasted	after meal	ratio	90%confidence interval
Cmax	(ng/mL)	447 ± 130 / 431	555 ± 112 / 544	1.264	1.160 – 1.378
tmax	(h)	8.88 ± 2.42 / 8.54	8.83 ± 1.01 / 8.78		
AUC(0-t)	(ng*h/mL)	11537 ± 5168 / 10720	11411 ± 3229 / 10998	1.026	0.940 – 1.120
AUC(0-T)	(ng*h/mL)	10086 ± 3553 / 9606	10385 ± 2386 / 10130	1.054	0.978 – 1.137
AUC(0-∞)	(ng*h/mL)	12370 ± 5454 / 11530	12062 ± 3288 / 11659	1.011	0.930 – 1.100
t1/2	(h)	18.5 ± 4.95 / 17.8	15,8 ± 3.07 / 15.5		

For the immediate release tablet, the propiverine concentration profiles obtained for the immediate release tablet reached significantly higher propiverine peaks about 0.5 hours later compared to the administration under fasting conditions.

For the modified release formulation, the results of the pharmacokinetic evaluation of Propiverine profiles following the modified release capsule under fasting conditions and after meal did not reveal any relevant difference demonstrating that there is no food effect for the modified release formulation.

Overall, the results suggest that food does not have a significant effect on the concentration and extent of exposure of propiverine.

Special populations
This has previously been described. Reference is made to Aponorm XL 30 mg Modified-Release Capsules, (PL 15072/0017; UK/H/6097/001/DC).

In terms of special populations, systemic exposure of propiverine was found to be higher in patients with severe renal impairment. However, the mean terminal elimination rate constant was found to be within the pre-specified criteria and did not exceed 2, suggesting that renal impairment did not alter elimination and metabolism. Therefore, no dose-adjustment is considered necessary for the 30 mg modified release formulation as the dose proposed is once daily. The rationale provided regarding this is considered acceptable. For subjects with hepatic impairment, it appears that only subjects with mild and moderate hepatic impairment were investigated. Overall, the results suggest that no dose adjustment is considered necessary in patients with mild to moderate hepatic impairment.

There does not appear to be gender related or race related differences in pharmacokinetics parameters. In addition, there does not seem to be any differences in pharmacokinetics parameters as a result of increase in age.

Conclusion of pharmacokinetic studies
The pharmacokinetics of propiverine has been adequately characterised. There are no particular issues to highlight.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted in support of this application and none were required as the pharmacodynamic properties of propiverine are well-known. Reference is made to Aponorm XL 30 mg Modified-Release Capsules (PL 15072/0017; UK/H/6097/001/DC).

IV.4 Clinical Efficacy
The efficacy of propiverine is well known and established.

Considering the dose-linearity and the proof of efficacy of the 30 mg modified release capsule in a placebo-controlled, non-inferiority trial, no further study was conducted with the 45 mg modified release capsule in patients with overactive bladder syndrome.

In terms of the proposed overactive bladder indication, reference is made to Aponorm XL 30 mg modified release capsules, (PL 15072/0017 UK/H/6097/001/DC); a summary of the submitted efficacy studies is provided below.

Pivotal efficacy study 1
A double-blind, double dummy, randomised, placebo-controlled parallel groups, multicentre study conducted to compare the efficacy and tolerability of Propiverine hydrochloride immediate (IR) and modified release (Aponorm) in the treatment of patients with overactive bladder.

Female and male patients ≥18 years of age with overactive bladder who: had at least 2 incontinence episodes within 3 days and had at least 10 micturition within 24 hours were enrolled into the study.

The primary efficacy variable was the number of incontinence episodes within 24 hours.

Secondary endpoints were the number of micturition within 24 hours and urge episodes within 24 hours, for 3 consecutive days during screening period (days –6 to –1) and at the end of treatment phase (days 29 to 31).

In addition, a Quality of life questionnaire (King's Health Questionnaire) was administered. This was completed by the patients prior to therapy (Visit 2) and after therapy (Visit 4).

Results
The results for the primary efficacy variable (number of incontinence episodes) are summarised below:

In the pooled cohorts, the End of Treatment (EoT) mean were 1.1 episodes in the propiverine immediate release group, 0.9 episodes in the propiverine modified release group and 1.7 episodes in the placebo group. The mean improvement were 2.3 episodes in the propiverine immediate release group, 2.5 episodes in the propiverine modified release group and 1.8 episodes in the placebo group.

In the pooled cohorts, non-inferiority of propiverine modified release to propiverine immediate release was shown. The estimated difference in the LS means was –0.20 with a 95% CI of –0.43 to 0.03. Superiority of propiverine immediate release over placebo was shown, the estimated difference in the LS means was 0.57 with a 95% CI of 0.22 to 0.92. Superiority of propiverine modified release over placebo was also shown, the estimated difference in the LS means was 0.77 with a 95% CI of 0.44 to 1.10.

The results of the secondary endpoints of efficacy were in line with the results of the primary efficacy variable for almost all the comparisons:

- the number of micturition within 24 hours was statistically significantly more reduced in both propiverine groups than in the placebo group but the difference between the two propiverine groups was not statistically significant

- the number of urge episodes within 24 hours was statistically significantly more reduced in both propiverine groups than in the placebo group but the difference between the two propiverine groups was not statistically significant

- the mean volume of the single micturition was statistically significantly more increased in both propiverine groups than in the placebo group but the difference between the two propiverine groups was not statistically significant

- For the King’s health questionnaire results in cohort II, the overall comparison of the differences in change was statistically significant for parts I and II in favour of propiverine, but not for the total score (p=0.0461, 0.0323 and 0.0516, respectively). In the pooled cohorts, these results were p=0.0090, 0.0679 and 0.0894, respectively.

The investigators rated the overall efficacy as moderate or better for most of the patients.

Conclusion of Pivotal efficacy study 1
The results demonstrated that for the primary endpoints, there was a reduction in the number of incontinence episodes. The difference between the immediate release formulation and the modified release/ modified release formulation compared with placebo was statistically significant.

In terms of the mean number of micturition per 24 hours; there was a reduction in micturition frequency in all the groups. The difference compared to placebo was statistically significant for both the immediate release formulation and the modified release formulation.

For the other secondary endpoints; the changes from baseline were comparable across all the treatment groups. And the differences compared to placebo were all statistically significant.

In terms of the quality of life scores, both the immediate release and the modified release showed improvement in most of the domains.

Pivotal efficacy study 2
A randomised, double-blind, double-dummy, multi-centre clinical study to evaluate the safety and efficacy of propiverine hydrochloride modified release capsule (Aponorm) for the treatment of overactive bladder with tolterodine modified release tablet as active control.

Study Objective
To evaluate the efficacy and safety of propiverine hydrochloride modified release capsule in the treatment of overactive bladder in Chinese population with urgency, urinary frequency and/or urge urinary incontinence.

The primary objective was to measure the change in mean micturition frequency/24h on the basis of continuous 3-day record, prior to medication and after 8 weeks of medication.

Secondary objectives were to measure the following:
- the change of mean number of incontinence episodes/24 h on the basis of continuous 3-day record, prior to medication, after 2 weeks and 8 weeks of medication,
- the change of mean micturition frequency/24 h on the basis of continuous 3-day record, prior to medication and after 2 weeks of medication
- the change of the mean voided volume based on continuous 3-day record, prior to medication, after 2 weeks and 8 weeks of medication
- Patient's feeling of treatment benefit
- Time of onset of drug action

A total of 80 male patients and 244 female patients with an average age of 50 years were enrolled into the study

Patients with disease characteristics, n (%)	Tolterodine tartrate extended release tablet group (N=162)	Propiverine hydrochloride extended release capsule group (N=162)	p-value
Urinary frequency	162 (100.0%)	162 (100.0%)	-
Urgency	155 (95.7%)	155 (95.7%)	-
Urinary incontinence	48 (29.6%)	60 (37.0%)	0.1573
Urge urinary incontinence	41 (25.3%)	47 (29.0%)	0.4536
Mixed urinary incontinence	7 (4.3%)	13 (8.0%)	0.1660
Mean micturition frequency/24 h (Mean± SD)	14.65 ± 6.04	15.17 ± 5.80	0.2132
Mean number of incontinence	0.62 ± 1.56	1.26 ± 3.08	0.2251

Outcomes and estimation
- After 8 weeks of medication, mean micturition frequency/24 h of both tolterodine tartrate modified release tablet group and propiverine hydrochloride modified release capsule group were significant reduced from baseline ($p<0.0001$).
- After controlling centre effect and baseline effect, both FAS and PPS showed that there was no statistical significance difference between the two groups after 8 weeks of treatment ($p>0.05$).

- PPS showed that mean of the differences (control group – test group) were -0.42 and 95%CI was [－1.20, 0.35],
- After 2 weeks and 8 weeks of medication, mean number of incontinence episodes/24 h and mean volume of single micturition in both groups showed significant improvement from baseline ($p<0.05$). Difference of the change of mean number of incontinence episodes/24 h between the groups was statistical significant ($p<0.05$).
- There was no statistically significant difference on patient's assessment of benefit and benefit level between the two groups. However, after 6 weeks and 8 weeks of medication, FAS showed that a higher percentage of patients did benefit from treatment in the propiverine hydrochloride modified release capsule group than in the tolterodine tartrate modified release tablet group ($p<0.05$).

Change of mean micturition frequency/24 h (FAS)

Parameter / Statistic		Tolterodine tartrate extended release tablet group	Propiverine hydrochloride extended release capsule group	Statistic	p-value
Baseline	N (missing)	162 (0)	162 (0)	-1.2448	0.2132
	Mean ± SD	14.65 ± 6.04	15.17 ± 5.80		
	Median	13.00	13.50		
	Q1; Q3	10.67; 16.33	11.33; 17.67		
	Min; Max	8.33; 48.67	7.33; 48.00		
14th day of treatment	N (missing)	162 (0)	162 (0)	-1.1718	0.2413
	Mean ± SD	11.88 ± 4.90	12.22 ± 4.77		
	Median	10.33	11.67		
	Q1; Q3	8.67; 14.33	8.67; 14.67		
	Min; Max	4.67; 30.33	5.33; 41.67		
56th day of treatment	N (missing)	162 (0)	162 (0)	0.4825	0.6295
	Mean ± SD	10.88 ± 4.76	10.59 ± 4.46		
	Median	10.00	9.67		
	Q1; Q3	7.67; 13.33	7.33; 12.67		
	Min; Max	4.00; 35.67	4.67; 34.67		
Change from baseline to 14th day of treatment	N (missing)	162 (0)	162 (0)	-1.3465	0.1781
	Mean ± SD	2.78 ± 4.01	2.95 ± 3.00		
	Median	2.00	2.67		

Conclusion Pivotal efficacy Study 2

The results showed that for the primary endpoint, there was a change in micturition frequency from baseline for both tolterodine and the modified release formulation. In terms of the secondary endpoints, the changes from baseline were comparable for both tolterodine and the modified release formulation and the differences compared to placebo were all statistically significant.

Overall the modified release formulation was demonstrated to be non-inferior to tolterodine.

Supportive studies - immediate release formulation

Since the modified release formulation under consideration was developed as a line-extension to the propiverine immediate formulation, the summaries of studies conducted with the immediate release formulation have been included as supportive information.

Supportive Study 1

A randomised, double-blind, multicentre, controlled, parallel-group study, was conducted to evaluate the efficacy and safety of propiverine hydrochloride in comparison to oxybutynin in patients with urge-incontinence. The results showed a decrease in the frequency of micturition and episodes of urgency in both the propiverine and oxybutynin group. This however was not statistical significant when compared to placebo.

Supportive Study 2
A double-blind, randomised, parallel group study, was conducted to investigate the tolerance (in particular with regard to induction of heart-rate disturbances) and effectiveness of propiverine 15 mg immediate release formulation in comparison to placebo in the treatment of urgency in the elderly. The results demonstrated a reduction in the frequency of micturition and number of urge incontinence episodes in the propiverine which was statistically significant when compared to placebo.

In conclusion, it is considered that the efficacy of the modified release 45 mg formulation is adequately demonstrated. There are no issues to highlight.

IV.5 Clinical Safety

Since Aponorm XL 45 mg is a line-extension to propiverine MR 30 mg, safety-related data already presented in the previous DCP (UK/H/6097/01/DC) are considered relevant to support safety of propiverine MR 45 mg. Furthermore, safety of propiverine up to a daily dose of 45 mg was already evaluated in terms of propiverine MR 30 mg in patients with overactive bladder (OAB). Thus, reference is made to the appropriate clinical documentation (UK/H/6097/01/DC).

In addition, the application for Aponorm XL 45 mg is supported by the safety data generated from the following:

- Non-interventional studies (NISs) with propiverine modified release 45 mg in overactive bladder patients
- Supportive randomised clinical trials with propiverine IR 15 mg in patients with overactive bladder and urinary incontinence

The safety profile of propiverine is considered to be adequately characterised. No new significant safety concerns have been identified.

The adverse event profile is generally in line with other anti-muscarinic agents and includes gastrointestinal side effects, dry mouth and ocular disorders.

IV.6 Risk Management Plan

The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aponorm XL 45 mg.

A summary of safety concerns is listed in the table below:

Summary of Safety concerns

Important identified risks	• Hallucination • Urinary retention • Anti-cholinergic effects (eye): angle closure glaucoma • Anti-cholinergic effects (cardiovascular): tachycardia
Important potential risks	• Anticholinergic effects (gastrointestinal): faecaloma, subileus
Missing information	• Use in patients with impaired hepatic function • Use in pregnant and breast-feeding women • Use in patients concomitantly receiving potent CYP 3A4 inhibitors such as azole antifungals or macrolide antibiotics

Routine pharmacovigilance and risk minimisation activities, which are considered acceptable, are planned for all safety concerns.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Aponorm XL 45 mg, from a clinical point of view.

V. USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

The benefit:risk for propiverine hydrochloride is well-known for the proposed indication: in adults for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder. Sufficient clinical information has been submitted to support this application

Taking the overall evidence on efficacy and safety, the RMS is of the opinion that the benefit-risk profile for Aponorm XL 45 mg modified release in the proposed use is favourable.

The grant of a Marketing Authorisation is, therefore, recommended.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is presented below:

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up to the regulatory authorities for approval before packs are marketed. The current labelling text is presented below:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Aponorm XL 45 mg Modified Release Capsules
Propiverine hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each modified release capsule contains 45 mg propiverine hydrochloride (equivalent to 40.92 mg propiverine).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

7 modified release capsules
14 modified release capsules
20 modified release capsules
28 modified release capsules
30 modified release capsules
49 modified release capsules
50 modified release capsules
56 modified release capsules
60 modified release capsules
84 modified release capsules
98 modified release capsules
100 modified release capsules
112 modified release capsules
280 modified release capsules

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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S) , IF NECESSARY

8. EXPIRY DATE

Expiry date:

9. SPECIAL STORAGE CONDITIONS

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

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

APOGEPHA Arzneimittel GmbH
Kyffhäuserstraße 27
01309 Dresden
Germany

12. MARKETING AUTHORISATION NUMBER (S)

PL 15072/0018

13. BATCH NUMBER

Batch number:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use only as directed by a doctor.
Do not crush or chew.

16. INFORMATION IN BRAILLE

APONORM XL 45 MG

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

<PC: {number}
SN: {number}
NN: {number}>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC/PVDC/ALUMINIUM BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Aponorm XL 45 mg Modified Release Capsules

Propiverine hydrochloride

2. NAME OF THE MARKETING AUTHORISATION HOLDER

APOGEPHA Arzneimittel GmbH

3. EXPIRY DATE

Expiry date:

4. BATCH NUMBER

Batch number:

5. OTHER

<e.g. calender days>

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)