

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Aponorm XL 45 mg modified release capsules

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: Lactose monohydrate (8.5 mg)

For the full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Modified release capsule, hard

Orange size 2 capsules containing white to off-white pellets.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Aponorm XL 45 mg modified release capsules are indicated in adults for the symptomatic treatment of urinary incontinence and/or increased urinary frequency and urgency in patients with overactive bladder.

#### 4.2 Posology and method of administration

##### Posology

The recommended daily doses are as follows:

**Adults:** One capsule daily in adults with severe symptoms of OAB or without sufficient response to 30 mg modified-release capsules.

The maximum daily dose is one capsule daily.

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

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

It is recommended to re-evaluate effectiveness of the product beyond 4 weeks of treatment (see section 5.1).

#### Use in renal impairment

In patients with mild or moderate impairment of renal function, no dose adjustment is required (see section 4.4 and 5.2).

Aponorm XL 45 mg modified-release capsules is contra-indicated in patients with severe renal impairment (creatinine clearance < 30 ml/min), (see section 4.3 and 5.2).

#### Use in hepatic impairment

In patients with mild impaired hepatic function, there is no need for dose adjustment; however, treatment should proceed with caution. The treatment of patients with moderate to severe impairment is contraindicated because no data are available (see section 4.3 and 5.2).

#### Method of administration

Capsules for oral use.

Do not crush or chew the capsules.

There is no clinically relevant effect of food on the pharmacokinetics of Aponorm XL 45 mg modified-release capsules (see section 5.2). Accordingly, there is no particular recommendation for the intake of Aponorm XL 45 mg in relation to food.

### **4.3 Contraindications**

Aponorm XL 45 mg modified-release capsules are contraindicated in patients with the following:

- hypersensitivity to the active substance or any of the excipients listed in section 6.1
- 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
- severe renal impairment (creatinine clearance < 30 ml/min)
- tachyarrhythmias

### **4.4 Special warnings and precautions for use**

The drug should be used with caution in patients suffering from:

- autonomic neuropathy
- renal impairment (see section 4.2)
- hepatic impairment (see section 4.2)

Symptoms of the following diseases may be aggravated following administration of the drug:

- severe congestive heart failure (NYHA IV)
- prostatic enlargement
- hiatus hernia with reflux oesophagitis
- cardiac arrhythmia
- tachycardia

#### Angle-closure glaucoma

Propiverine, like other anticholinergics, induces mydriasis. Therefore, the risk to induce acute angle-closure glaucoma in individuals predisposed with narrow angles of the anterior chamber may be increased. Drugs of this class, including propiverine, have been reported to induce or precipitate acute angle-closure glaucoma.

Pollakiuria and nocturia due to renal disease or congestive heart failure, as well as organic bladder diseases (e.g. urinary tract infections, malignancy), should be ruled out prior to treatment.

Monitoring is recommended especially in first few months after initiating therapy or increasing the dose; consider discontinuing therapy or reducing the dose if serious anticholinergic CNS effects develop.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## **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 (if applied systemically), amantadine, neuroleptics (e.g. phenothiazines) and beta-adrenoceptor agonists (beta-sympathomimetics).
- Decreased effects due to concomitant medication with cholinergic drugs.
- Reduced blood pressure in patients treated with isoniazid.
- The effect of prokinetics such as metoclopramide may be decreased.

- Pharmacokinetic interactions are possible with other drugs metabolised by cytochrome P450 3A4 (CYP 3A4). However, a very pronounced increase of concentrations for such drugs is not expected as the effects of propiverine are small compared to classical enzyme inhibitors (e.g. ketoconazole or grapefruit juice). Propiverine may be considered as weak inhibitor of CYP 3A4. Pharmacokinetic studies with patients concomitantly receiving potent CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole) or macrolide antibiotics (e.g. erythromycin, clarithromycin) have not been performed.
- Patients receiving concomitant treatment with drugs that are potent inhibitors of CYP 3A4 combined with methimazole.

## **4.6 Fertility, pregnancy and lactation**

### Pregnancy

There are no data from the use of propiverine in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3).

Aponorm XL 45 mg is not recommended during pregnancy and in women of childbearing potential not using contraception.

### Breastfeeding

It is unknown whether propiverine or metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of propiverine or metabolites in milk (for details see section 5.3).

A risk to the newborns or infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Aponorm XL 45 mg therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### Fertility

There are no human data on the effect of propiverine on fertility.

Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

## **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

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

Sedative drugs may enhance the drowsiness caused by propiverine.

## 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 ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data).

All undesirable effects are transient and recede after a dose reduction or termination of the therapy after maximum 1-4 days.

### **Immune system disorders**

Rare: hypersensitivity

### **Psychiatric disorders**

Very rare: restlessness, confusion

Not known: hallucination

### **Nervous system disorders**

Common: headache

Uncommon: tremor, dizziness, dysgeusia

Not known: speech disorder

### **Eye disorders**

Common: accommodation disorder, visual impairment

### **Cardiac disorders**

Rare: tachycardia

Very rare: palpitation

### **Vascular disorders**

Uncommon: decreased blood pressure with drowsiness, flushing

### **Gastrointestinal disorders**

Very common: dry mouth

Common: constipation, abdominal pain, dyspepsia

Uncommon: nausea/vomiting

#### **Skin and subcutaneous tissue disorders**

Uncommon: pruritus

Rare: rash

#### **Renal and urinary disorders**

Uncommon: urinary retention, bladder and urethral symptoms

#### **General disorders and administration site conditions**

Common: fatigue

During long-term therapy hepatic enzymes should be monitored, because reversible changes of liver enzymes might occur in rare cases.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Yellow Card Scheme.

Website: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

### Symptoms:

Overdose with the muscarinic receptor antagonist propiverine can potentially result in severe anticholinergic effects. Peripheral and central nervous system disturbances may occur, such as:

- severe dry mouth
- bradycardia, possibly leading to tachycardia in the further course
- mydriasis and accommodation disorder
- urinary retention
- inhibition of intestinal motility
- restlessness, confusion, hallucination, confabulation
- dizziness, nausea, speech disorder, muscular weakness

### Treatment:

- In the event of overdose with propiverine the patient should be treated with activated charcoal suspension with plenty amount of water.
- Gastric lavage should only be taken into consideration with protective intubation, use of an oiled tube (dryness of mucosa) and if performed within 1 hour after ingestion of propiverine. Vomiting must not be induced.
- Forced diuresis or hemodialysis is not effective to enhance the renal elimination.
- In case of severe central anticholinergic effects such as hallucinations or pronounced excitation antidote treatment with physostigmine can be attempted.
- Convulsion or pronounced excitation: treatment with benzodiazepines
- Respiratory insufficiency: treatment with artificial respiration
- Urinary retention: treatment with catheterization
- Mydriasis: treatment with pilocarpine eye drops and/or darkening of the patient's room

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

ATC code: G04BD06

Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence

#### Mechanism of action

Inhibition of calcium influx and modulation of intracellular calcium in urinary bladder smooth muscle cells causing musculotropic spasmolysis.

Inhibition of the efferent connection of the nervus pelvici due to anticholinergic action.

#### Pharmacodynamic effects

In animal models propiverine hydrochloride causes a dose-dependent decrease of the intravesical pressure and an increase in bladder capacity.

The effect is based on the sum of the pharmacological properties of propiverine and three active urinary metabolites as shown in isolated detrusor strips of human and animal origin.

#### Clinical efficacy

Efficacy of Aponorm XL 45 mg was established in two open-label non-interventional studies in patients with overactive bladder (OAB).

A non-interventional study investigated the effectiveness and tolerability of flexible dosing of Aponorm XL 45 mg und 30 mg in 1335 OAB patients up to 12-weeks. The

results showed that dose adjustment can compensate initially inadequate effectiveness in patients with partial improvement in OAB symptoms (key results in Table 1).

Table 1 Summary of key results [mean (SD)] of a non-interventional study after 12 weeks of treatment

Visits	Dose before/after visit 2					
	30 mg / 30 mg	p <sup>*1</sup>	30 mg / 45 mg	p <sup>*2</sup>	45 mg / 45 mg	p <sup>*3</sup>
<b>Number of voidings/24 h</b>						
Baseline (BL)	13.3 (4.3)		14.6 (4.8)		14.4 (4.3)	
After 4 weeks (4wk)	8.8 (2.8)		11.4 (4.3)		9.5 (3.3)	
End of Treatment (EoT)	7.6 (2.4)		9.0 (3.7)		8.1 (3.0)	
Difference 4wk-BL	-4.5 (3.5)	<0.0001	-3.2 (2.9)	<0.0001	-5.0 (3.4)	0.0022
Difference EoT-BL	-5.6 (3.8)	0.7954	-5.5 (4.0)	0.0221	-6.4 (3.9)	0.0023
<b>Number of urgency episodes/24 h</b>						
Baseline (BL)	9.9 (6.3)		11.8 (6.8)		11.3 (5.9)	
After 4 weeks (4wk)	4.4 (3.9)		8.1 (5.6)		4.9 (3.6)	
End of Treatment (EoT)	2.8 (3.3)		4.6 (4.6)		3.1 (3.4)	
Difference 4wk-BL	-5.4 (4.6)	< 0.0001	-3.7 (4.4)	< 0.0001	-6.3 (4.9)	0.0104
Difference EoT-BL	-6.8 (5.3)	0.60	-7.2 (5.7)	0.10	-7.9 (5.7)	0.0032
<b>Number of incontinence episodes/24 h</b>						
Baseline (BL)	3.1 (3.6)		4.4 (4.8)		4.8 (4.6)	
After 4 weeks (4wk)	1.2 (3.0)		2.9 (3.6)		1.8 (1.4)	
End of Treatment (EoT)	0.6 (1.3)		1.6 (2.9)		1.0 (1.9)	
Difference 4wk-BL	-1.8 (3.7)	0.0820	-1.4 (2.2)	< 0.0001	-3.1 (3.9)	< 0.0001
Difference EoT-BL	-2.4 (3.1)	0.29	-2.6 (3.5)	0.0126	-3.6 (3.9)	< 0.0001

\*The Wilcoxon two-sample test was used to assess whether values of effectiveness differed between the subgroups.

<sup>1</sup> 30 mg / 30 mg vs. 30 mg / 45 mg; <sup>2</sup> 30 mg / 45 mg vs. 45 mg / 45 mg <sup>3</sup> 30 mg / 30 mg vs. 45 mg / 45 mg

Overall, all voiding parameters improved and about 90% of patients reported on an improvement regarding the Patient Perception of Bladder Control Score.

In another non-interventional study, long-term treatment with Aponorm XL 45 mg and 30 mg was evaluated in 363 patients with OAB. All effectiveness variables deriving from the bladder diary improved during the study conduct of 12 weeks (p<0.001) and remained stable or even further improved until the end of the long-term assessment after 24 weeks.

In addition, one pivotal double-blind placebo-controlled clinical trial was conducted to demonstrate the efficacy of Aponorm XL 30 mg for the treatment of overactive bladder in comparison to placebo and active comparator (see key results in the table below).

Table 2 Summary of key results (mean) of a randomized, double-blind, placebo- and active controlled clinical trial after 4 weeks of treatment

*Table 2 Summary of key results (mean) of a randomized, double-blind, placebo- and active controlled clinical trial after 4 weeks of treatment*

	<b>Aponorm XL 30 mg (N=363)</b>	<b>Placebo (N=187)</b>	<b>Active comparator* (N=360)</b>
<b>Number of incontinence episodes/24 hours</b>			
Baseline (BL)	3.4	3.5	3.4
End of Treatment (EoT)	0.9	1.7	1.1
Difference EoT-BL	-2.5	-1.8	-2.3
p-value**	<0.0001		0.0001
<b>Number of micturitions/24 hours</b>			
Baseline (BL)	12.7	13.4	12.8
End of Treatment (EoT)	9.1	10.3	9.1
Difference EoT-BL	-3.6	-3.0	-3.7
p-value**	0.0002		0.0002
<b>Number of urge episodes/24 hours</b>			
Baseline (BL)	6.4	6.1	6.1
End of Treatment (EoT)	3.8	4.4	4.1
Difference EoT-BL	-2.9	-1.9	-2.5
p-value**	0.0028		0.1106

\* propiverine hydrochloride 15 mg coated tablets (b.i.d.)

\*\* versus placebo

## 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 XL 45 mg, propiverine is absorbed from the gastrointestinal tract with maximal plasma concentrations reached after 9.9 hours. The mean absolute bioavailability of Aponorm XL 45 mg is  $59.5 \pm 23.3\%$  (arithmetic mean value  $\pm$  SD for  $AUC_{0-\infty}$  (p.o.) /  $AUC_{0-\infty}$  (i.v.)).

Food does not influence the pharmacokinetics of propiverine.

The bioavailability of propiverine after the meal was 99 % compared to the fasting conditions. Administration of the ER capsule leads to mean C<sub>max</sub> – concentrations of propiverine of about 70 ng/ml reached within 9.5 hours after administration.

The C<sub>max</sub> values for the main metabolite propiverine-N-oxide were slightly increased by food (f = 1.26), whereas the extent of absorption was unchanged.

Propiverine-N-oxide showed for all pharmacokinetic parameters 90 % confidence intervals within the acceptance ranges.

An adjustment of dose in relation to food intake is not required.

### Distribution

After administration of Aponorm XL 45 mg, steady state is reached after four to five days at a higher concentration level than after single dose application (Coverage = 71 ng/ml).

The volume of distribution was estimated in 21 healthy volunteers after intravenous administration of propiverine hydrochloride to range from 125 to 473 l (mean 279 l) indicating, that a large amount of available propiverine is distributed to peripheral compartments. The binding to plasma proteins is 90 - 95 % for the parent compound and about 60 % for the main metabolite.

*Table 3 Pharmacokinetic characteristics (geometric mean, ±SD, range) of propiverine in 10 healthy volunteers after single dose administration of Aponorm XL 30 mg and Aponorm XL 45 mg modified release capsules:*

<b>Dose [mg]</b>	<b>30</b>	<b>45</b>
AUC <sub>0-∞</sub> [ng·h/ml]	1378 (903, 2104)	1909 (1002, 3639)
C <sub>max</sub> [ng/ml]	60.6 (41.5, 88.6)	80.0 (41.8, 152.1)
t <sub>1/2</sub> [h]	14.2 (10.8, 18.6)	16.3 (13.9, 19.2)
t <sub>max</sub> [h]	9.9 ± 2.4	9.9 ± 2.4

*Figure 1 Plasma concentrations of propiverine in 10 healthy volunteers after single dose administration of Aponorm XL 30 mg and Aponorm XL 45 mg modified release capsules:*

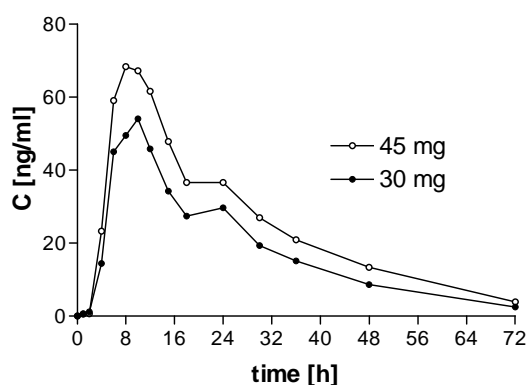
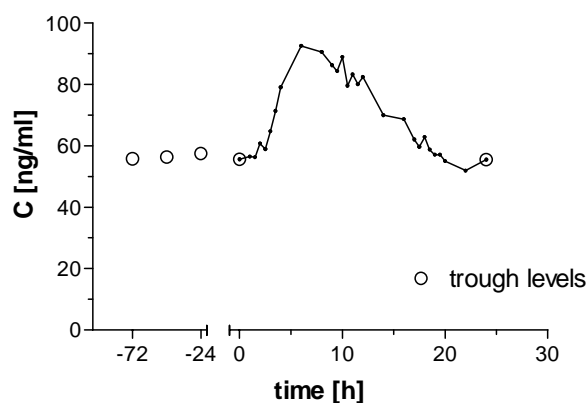


Table 4 Steady state characteristics of propiverine following multiple-dose administration to 24 healthy volunteers of Aponorm XL 45 mg modified release capsules once daily for 7 days:

	geometric mean	range or $\pm$ SD
AUC <sub>0-24h</sub> [ng·h/ml]	1711	1079, 2713
PTF [%]	109.4	81.2, 147.5
C <sub>av</sub> [ng/ml]	71	45.0, 113.0
C <sub>max</sub> [ng/ml]	105	71, 155
C <sub>min</sub> [ng/ml]	29	20, 42
t <sub>1/2</sub> [h]	20.4	12.8, 32.3
t <sub>max</sub> [h]	7.3	$\pm$ 2.5

PTF: peak-trough fluctuation

Figure 2 Plasma concentrations of propiverine on day 7 and trough levels during treatment following multiple-dose administration of Aponorm XL 45 mg modified release capsules to 24 healthy volunteers once daily for 7 days:



### 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-containing monooxygenases (FMO) 1 and 3 and leads to the formation of the much less active N-oxide, the plasma concentration of which greatly

exceeds that of the parent substance. Four metabolites were identified in urine; three of them are pharmacologically active and may contribute to the therapeutic efficacy.

In vitro there is a slight inhibition of CYP 3A4 and CYP 2D6 detectable which occurs at concentrations exceeding therapeutic plasma concentrations 10- to 100-fold (see section 4.5).

#### Elimination

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

#### Linearity/ non-linearity

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

Figure 3 Correlation between the oral dose of extended release propiverine and the resulting  $AUC_{0-\infty}$ :

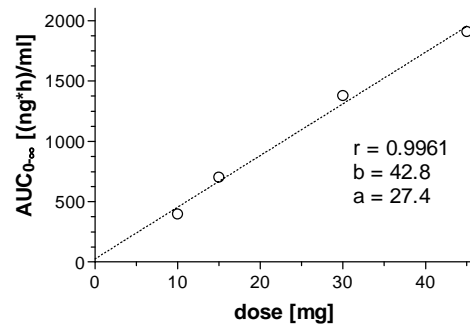
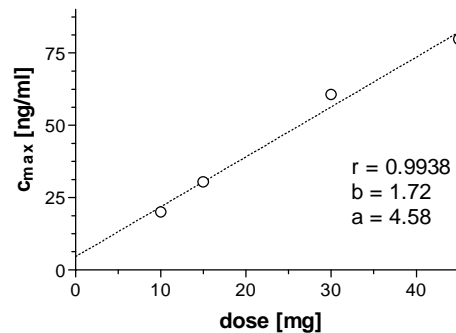


Figure 4 Correlation between the oral dose of extended release propiverine and the resulting  $C_{max}$ :



### 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. However, in patients with severe renal impairment (creatinine clearance < 30 ml/min) the maximum daily dose of propiverine is 30 mg. Aponorm XL 45mg modified release capsules are not recommended in patients with severe renal failure.

#### *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 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. As bioequivalence of propiverine hydrochloride 15 mg coated tablets t.i.d. and propiverine hydrochloride 45 mg modified release capsules s.i.d. was established in a GCP compliant study the same can be concluded for Aponorm XL 45 mg.

#### *Patients with glaucoma:*

The treatment with Aponorm XL 45 mg will not lead to an increase of intraocular pressure in patients with open angle glaucoma and in patients with treated

(controlled) angle closure glaucoma. This was shown in two placebo-controlled studies with propiverine hydrochloride 15 mg coated tablets t.i.d. over 7 days.

### **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.

No effects on male and female fertility and reproduction behaviour were observed in toxicological studies with rats.

In animal studies, skeletal retardation in the offspring occurred when the drug was administered orally at high doses to pregnant females. In lactating mammals propiverine was excreted into the milk.

There was no evidence of mutagenicity. The carcinogenicity study in mice demonstrated an increased incidence of hepatocellular adenoma and carcinoma in high dose males. In the rat carcinogenicity study hepatocellular adenoma, kidney adenoma and urinary bladder papilloma has been demonstrated in high dose male rats, while in female animals endometrial stromal polyps were increased at the high dose levels. Both the rat and mouse tumours were considered to be species specific and therefore not of clinical relevance.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Pellets

- 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.

#### Capsule

- Gelatine,
- Titanium dioxide E171,

- red iron oxide E172,
- yellow iron oxide E172.

## **6.2 Incompatibilities**

not applicable

## **6.3 Shelf life**

4 years

## **6.4 Special precautions for storage**

Store in the original package to protect from moisture.

Do not store above 30 °C.

## **6.5 Nature and contents of container**

Blisters of PVC/PVDC and aluminium foil in cartons of 7, 14, 20, 28, 30, 49, 50, 56, 60, 84, 98, 100, 112 or 280 capsules.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

not applicable

## **7 MARKETING AUTHORISATION HOLDER**

APOGEPHA Arzneimittel GmbH,  
Kyffhäuserstraße 27,  
01309 Dresden,  
Germany

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 15072/0018

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

29/06/2023

**10 DATE OF REVISION OF THE TEXT**

28/01/2021