SAMENVATTING VAN DE PRODUCTKENMERKEN

1 NAME OF THE MEDICINAL PRODUCT

Agomelatine betapharm 25 mg filmomhulde tabletten

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains agomelatine-citric acid cocrystal equivalent to 25 mg of agomelatine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).
Yellow, oblong, biconvex film-coated tablets 9 mm long, 4.5 mm wide.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Agomelatine is indicated for the treatment of major depressive episodes in adults.

4.2 Posology and method of administration

Posology
The recommended dose is 25 mg once daily taken orally at bedtime.
After two weeks of treatment, if there is no improvement of symptoms, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets, taken together at bedtime.

Decision of dose increase has to be balanced with a higher risk of transaminases elevation. Any dose increase to 50 mg should be made on an individual patient benefit/risk basis and with strict respect of liver function test (LFT) monitoring.

Liver function tests should be performed in all patients before starting treatment. Treatment should not be initiated if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4).
During treatment transaminases should be monitored periodically after around three weeks, six weeks (end of acute phase), twelve weeks and twenty-four weeks (end of maintenance phase) and thereafter when clinically indicated (see also section 4.4). Treatment should be discontinued if transaminases exceed 3 X upper limit of normal (see sections 4.3 and 4.4).
When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment.

Treatment duration
Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free of symptoms.

Switching therapy from SSRI/SNRI antidepressant to agomelatine
Patients may experience discontinuation symptoms after cessation from an SSRI/ SNRI

antidepressant.

The SmPC of the actual SSRI/SNRI should be consulted on how to withdraw the treatment to avoid this. Agomelatine can be started immediately while tapering the dosage of a SSRI//SNRI (see section 5.1).

Treatment discontinuation
No dosage tapering is needed on treatment discontinuation.

Special populations

Elderly
The efficacy and safety of agomelatine (25 to 50mg/day) have been established in elderly depressed patients (< 75years). No effect is documented in patients ≥75 years. Therefore, agomelatine should not be used by patients in this age group (see sections 4.4 and 5.1). No dose adjustment is required in relation to age (see section 5.2).

Renal impairment
No relevant modification in agomelatine pharmacokinetic parameters in patients with severe renal impairment has been observed. However, only limited clinical data on the use of Agomelatine in depressed patients with severe or moderate renal impairment with major depressive episodes is available. Therefore, caution should be exercised when prescribing Agomelatine to these patients.

Hepatic impairment
Agomelatine is contraindicated in patients with hepatic impairment (see sections 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of agomelatine in children from 2 years onwards for treatment of major depressive episodes have not yet been established. No data are available (see section 4.4).
There is no relevant use of agomelatine in children from birth to 2 years for treatment of major depressive episodes.

Method of administration
For oral use.
Agomelatine film-coated tablets may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Hepatic impairment (i.e. cirrhosis or active liver disease) or transaminases exceeding 3 X upper limit of normal (see sections 4.2 and 4.4).
Concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) (see section 4.5).

4.4 Special warnings and precautions for use

Monitoring of liver function
Cases of liver injury, including hepatic failure (few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors), elevations of liver enzymes exceeding 10 times upper limit of normal, hepatitis and jaundice have been reported in patients treated with agomelatine in the post-marketing setting (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage is predominantly hepatocellular with increased serum transaminases, which usually return to normal levels on cessation of agomelatine.

Caution should be exercised before starting treatment and close surveillance should be performed throughout the treatment period in all patients, especially if hepatic injury risk factors or concomitant medicinal products associated with risk of hepatic injury are present.

- *Before starting treatment*

Treatment with Agomelatine should only be prescribed after careful consideration of benefit and risk in patients with hepatic injury risk factors e.g.:

- obesity/overweight/non-alcoholic fatty liver disease, diabetes,
- alcohol use disorder and/or substantial alcohol intake

and in patients receiving concomitant medicinal products associated with risk of hepatic injury.

Baseline liver function tests should be undertaken in all patients and treatment should not be initiated in patients with baseline values of ALT and/or AST >3 X upper limit of normal (see section 4.3). Caution should be exercised when Agomelatine is administered to patients with pretreatment elevated transaminases (> the upper limit of the normal ranges and ≤3 times the upper limit of the normal range).

- *Frequency of liver function tests*

- before starting treatment
- and then:
    - after around 3 weeks,
    - after around 6 weeks (end of acute phase),
    - after around 12 and 24 weeks (end of maintenance phase),
    - and thereafter when clinically indicated.
- When increasing the dosage, liver function tests should again be performed at the same frequency as when initiating treatment.

Any patient who develops increased serum transaminases should have his/her liver function tests repeated within 48 hours.

- *During treatment period*

Agomelatine treatment should be discontinued immediately if:

- patient develops symptoms or signs of potential liver injury (such as dark urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, sustained new-onset and unexplained fatigue).
- the increase in serum transaminases exceeds 3 X upper limit of normal.

Following discontinuation of Agomelatine therapy liver function tests should be repeated until serum transaminases return to normal.

Use in paediatric population

Agomelatine is not recommended in the treatment of depression in patients under 18 years of age since safety and efficacy of Agomelatine have not been established in this age group. In clinical trials among children and adolescents treated with other antidepressants, suicide-related behaviour (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed compared to those treated with placebo (see section 4.2).

Elderly

No effect of agomelatine is documented in patients ≥75 years, therefore agomelatine should not be used by patients in this age group (see also sections 4.2 and 5.1).

Use in elderly with dementia
Agomelatine should not be used for the treatment of major depressive episodes in elderly patients with dementia since the safety and efficacy of Agomelatine have not been established in these patients.

Bipolar disorder/ mania / hypomania
Agomelatine should be used with caution in patients with a history of bipolar disorder, mania or hypomania and should be discontinued if a patient develops manic symptoms (see section 4.8).

Suicide/suicidal thoughts
Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.
Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressants in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo, in patients less than 25 years old.
Close supervision of patients and in particular those at high risk should accompany treatment especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted to the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Combination with CYP1A2 inhibitors (see sections 4.3 and 4.5)
Caution should be exercised when prescribing Agomelatine with moderate CYP1A2 inhibitors (*e.g.* propranolol, enoxacin) which may result in increased exposure of agomelatine.

- Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions affecting agomelatine
Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Medicinal products that interact with these isoenzymes may decrease or increase the bioavailability of agomelatine.

Fluvoxamine, a potent CYP1A2 and moderate CYP2C9 inhibitor markedly inhibits the metabolism of agomelatine resulting in a 60-fold (range 12-412) increase of agomelatine exposure.
Consequently, co-administration of Agomelatine with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.

Combination of agomelatine with oestrogens (moderate CYP1A2 inhibitors) results in a several fold increased exposure of agomelatine. While there was no specific safety signal in the 800 patients treated in combination with oestrogens, caution should be exercised when prescribing agomelatine with other moderate CYP1A2 inhibitors (e.g. propranolol, enoxacin) until more experience has been gained (see section 4.4).

Rifampicin an inducer of all three cytochromes involved in the metabolism of agomelatine may decrease the bioavailability of agomelatine.
Smoking induces CYP1A2 and has been shown to decrease the bioavailability of agomelatine, especially in heavy smokers (≥ 15 cigarettes/day) (see section 5.2).

Potential for agomelatine to affect other medicinal products
In vivo, agomelatine does not induce CYP450 isoenzymes. Agomelatine inhibits neither CYP1A2 *in vivo* nor the other CYP450 *in vitro*. Therefore, agomelatine will not modify exposure to medicinal products metabolised by CYP 450.

Other medicinal products
No evidence of pharmacokinetic or pharmacodynamic interaction with medicinal products which could be prescribed concomitantly with Agomelatine in the target population was found in phase I clinical trials: benzodiazepines, lithium, paroxetine, fluconazole and theophylline.

Alcohol
The combination of Agomelatine and alcohol is not advisable.

Electroconvulsive therapy (ECT)
There is no experience of concurrent use of agomelatine with ECT. Animal studies have not shown proconvulsant properties (see section 5.3). Therefore, clinical consequences of ECT performed concomitantly with Agomelatine treatment, are considered to be unlikely.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of agomelatine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of Agomelatine during pregnancy.

Breast-feeding
It is not known whether agomelatine/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of agomelatine/metabolites in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Agomelatine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Agomelatine has minor influence on the ability to drive and use machines. Considering that dizziness and somnolence are common adverse reactions, patients should be cautioned about their ability to drive or operate machines.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions were usually mild or moderate and occurred within the first two weeks of treatment. The most common adverse reactions were headache, nausea and dizziness.
These adverse reactions were usually transient and did not generally lead to cessation of therapy.

Tabulated list of adverse reactions
The below table gives the adverse reactions observed from placebo-controlled and active-controlled clinical trials.
Adverse reactions are listed below using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). The frequencies have not been corrected for placebo.

System organ class	Frequency	Preferred Term
Psychiatric disorders	Common	Anxiety
		Abnormal dreams*
	Uncommon	Suicidal thoughts or behaviour (see section 4.4)
		Agitation and related symptoms* (such as irritability and restlessness)
		Aggression*
		Nightmares*
		Mania/hypomania* These symptoms may also be due to the underlying disease (see section 4.4).
		Confusional state*
	Rare	Hallucinations*
Nervous system disorders	Very common	Headache
	Common	Dizziness
		Somnolence
		Insomnia
	Uncommon	Migraine
		Paraesthesia
		Restless leg syndrome*
	Rare	Akathisia*
Eye disorders	Uncommon	Blurred vision
Ear and labyrinth disorders	Uncommon	Tinnitus*
Gastrointestinal Disorders	Common	Nausea
		Diarrhoea
		Constipation
		Abdominal pain

		Vomiting*
Hepato-biliary disorders	Common	Increased ALT and/or AST (in clinical trials, increases >3 times the upper limit of the normal range for ALT and/or AST were seen in 1.2% of patients on agomelatine 25 mg daily and 2.6 % on agomelatine 50 mg daily vs. 0.5% on placebo).
	Uncommon	Increased gamma-glutamyltransferase* (GGT) (>3 times the upper limit of the normal range)
	Rare	Hepatitis
		Increased alkaline phosphatase* (>3 times the upper limit of the normal range)
		Hepatic failure*(1)
		Jaundice*
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis
		Eczema
		Pruritus*
		Urticaria*
	Rare	Erythematous rash
		Face oedema and angioedema*
Musculoskeletal and connective tissue disorders	Common	Back pain
	Uncommon	Myalgia*
Renal and urinary disorders	Rare	Urinary retention*
General disorders and administration site conditions	Common	Fatigue
Investigations	Common	Weight increased*
	Uncommon	Weight decreased*

* Frequency estimated from clinical trials for adverse reactions detected from spontaneous report
(1) Few cases were exceptionally reported with fatal outcome or liver transplantation in patients with hepatic risk factors.

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 Appendix V.

4.9 Overdose

Symptoms
There is limited experience with agomelatine overdose. Experience with agomelatine in overdose has indicated that epigastralgia, somnolence, fatigue, agitation, anxiety, tension, dizziness, cyanosis or malaise have been reported.

One person having ingested 2,450 mg agomelatine, recovered spontaneously without cardiovascular and biological abnormalities.

Management
No specific antidotes for agomelatine are known. Management of overdose should consist of treatment of clinical symptoms and routine monitoring. Medical follow-up in a specialised environment is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics, other antidepressants, ATC-code: N06AX22

Mechanism of action

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and 5-HT_{2C} antagonist. Binding studies indicate that agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors.
Agomelatine resynchronises circadian rhythms in animal models of circadian rhythm disruption. Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin.

Pharmacodynamic effects

Agomelatine has shown an antidepressant-like effect in animal models of depression (learned helplessness test, despair test, chronic mild stress) as well as in models with circadian rhythm desynchronisation and in models related to stress and anxiety.
In humans, agomelatine has positive phase shifting properties; it induces a phase advance of sleep, body temperature decline and melatonin onset.

Clinical efficacy and safety

The efficacy and safety of agomelatine in major depressive episodes have been studied in a clinical programme including 7,900 patients treated with agomelatine.

Ten placebo controlled trials have been performed to investigate the short term efficacy of agomelatine in major depressive disorder in adults, with fixed dose and/or dose up-titration. At the end of treatment (over 6 or 8 weeks), significant efficacy of agomelatine 25-50 mg was demonstrated in 6 out of the ten short-term double-blind placebo-controlled trials. Primary endpoint was change in HAMD-17 score from baseline. Agomelatine failed to differentiate from placebo in two trials where the active control, paroxetine or fluoxetine showed assay sensitivity. Agomelatine was not compared directly with paroxetine and fluoxetine as these comparators where added in order to ensure assay sensitivity of the trials. In two other trials, it was not possible to draw any conclusions because the active controls, paroxetine or fluoxetine, failed to differentiate from placebo. However, in these studies it was not allowed to increase the start dose of either agomelatine, paroxetine or fluoxetine even if the response was not adequate.

Efficacy was also observed in more severely depressed patients (baseline HAM-D $\geq$ 25) in all positive placebo-controlled trials.

Response rates were statistically significantly higher with agomelatine compared with placebo.

Superiority (2 trials) or non-inferiority (4 trials) has been shown in six out of seven efficacy trials in heterogeneous populations of depressed adult patients versus SSRI/SNRI (sertraline, escitalopram, fluoxetine, venlafaxine or duloxetine) The anti-depressive effect was assessed with the HAMD-17 score either as primary or secondary endpoint.

The maintenance of antidepressant efficacy was demonstrated in a relapse prevention trial. Patients responding to 8/10-weeks of acute treatment with open-label agomelatine 25-50 mg once daily were randomised to either agomelatine 25-50 mg once daily or placebo for further 6-months. Agomelatine 25- 50 mg once daily demonstrated a statistically significant superiority compared to placebo ($p=0.0001$) on the primary outcome measure, the prevention of depressive relapse, as measured by time to relapse. The incidence of relapse during the 6-months double-blind follow up period was 22% and 47% for agomelatine and placebo, respectively.

Agomelatine does not alter daytime vigilance and memory in healthy volunteers. In depressed patients, treatment with agomelatine 25 mg increased slow wave sleep without modification of REM (Rapid Eye Movement) sleep amount or REM latency. Agomelatine 25 mg also induced an advance of the time of sleep onset and of minimum heart rate. From the first week of treatment, onset of sleep and the quality of sleep were significantly improved without daytime clumsiness as assessed by patients.

In a specific sexual dysfunction comparative trial with remitted depressed patients, there was a numerical trend (not statistically significant) towards less sexual emergent dysfunction than venlafaxine for Sex Effects Scale (SEXFX) drive arousal or orgasm scores on agomelatine. The pooled analysis of trials using the Arizona Sexual Experience Scale (ASEX) showed that agomelatine was not associated with sexual dysfunction. In healthy volunteers agomelatine preserved sexual function in comparison with paroxetine.

Agomelatine had neutral effect on heart rate and blood pressure in clinical trials.

In a trial designed to assess discontinuation symptoms by the Discontinuation Emergent Signs and Symptoms (DESS) check-list in patients with remitted depression, agomelatine did not induce discontinuation syndrome after abrupt treatment cessation.
Agomelatine has no abuse potential as measured in healthy volunteer studies on a specific visual analogue scale or the Addiction Research Center Inventory (ARCI) 49 check-list.
A placebo-controlled 8-week trial of agomelatine 25-50mg/day in elderly depressed patients (≥ 65 years, N=222, of which 151 on agomelatine) demonstrated a statistically significant difference of 2.67 points on HAM-D total score, the primary outcome. Responder rate analysis favoured agomelatine. No improvement was observed in very elderly patients (≥75 years, N= 69, of which 48 on agomelatine). Tolerability of agomelatine in elderly patients was comparable to that seen in the younger adults.

A specific controlled, 3-week trial has been conducted in patients suffering from major depressive disorder and insufficiently improved with paroxetine (a SSRI) or venlafaxine (a SNRI). When treatment was switched from these antidepressants to agomelatine, discontinuation symptoms arose after cessation of the SSRI or SNRI treatment, either after abrupt cessation or gradual cessation of the previous treatment. These discontinuation symptoms may be confounded with a lack of early benefit of agomelatine.
The percentage of patients with at least one discontinuation symptom one week after the SSRI/SNRI treatment stop, was lower in the long tapering group (gradual cessation of the previous SSRI/SNRI within 2 weeks) than in the short tapering group (gradual cessation of the previous SSRI/SNRI within 1 week) and in the abrupt substitution group (abrupt cessation): 56.1%, 62.6 % and 79.8% respectively.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with reference medicinal product containing agomelatine in one or more subsets of the paediatric population in the treatment of major depressive episodes (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption and bioavailability

Agomelatine is rapidly and well (≥ 80%) absorbed after oral administration. Absolute bioavailability is low (< 5% at the therapeutic oral dose) and the interindividual variability is substantial. The bioavailability is increased in women compared to men. The bioavailability is increased by intake of oral contraceptives and reduced by smoking. The peak plasma concentration is reached within 1 to 2 hours.

In the therapeutic dose-range, agomelatine systemic exposure increases proportionally with dose. At higher doses, a saturation of the first-pass effect occurs.
Food intake (standard meal or high fat meal) does not modify the bioavailability or the absorption rate. The variability is increased with high fat food.

Distribution

Steady state volume of distribution is about 35 l and plasma protein binding is 95% irrespective of the concentration and is not modified with age and in patients with renal impairment but the free fraction is doubled in patients with hepatic impairment.

Biotransformation

Following oral administration, agomelatine is rapidly metabolised mainly via hepatic CYP1A2; CYP2C9 and CYP2C19 isoenzymes are also involved but with a low contribution.
The major metabolites, hydroxylated and demethylated agomelatine, are not active and are rapidly conjugated and eliminated in the urine.

Elimination

Elimination is rapid, the mean plasma half-life is between 1 and 2 hours and the clearance is high (about 1,100 ml/min) and essentially metabolic.
Excretion is mainly (80%) urinary and in the form of metabolites, whereas unchanged compound recovery in urine is negligible.
Kinetics are not modified after repeated administration.

Renal impairment

No relevant modification of pharmacokinetic parameters in patients with severe renal impairment has been observed (n=8, single dose of 25 mg), but caution should be exercised in patients with severe or moderate renal impairment as only limited clinical data are available in these patients (see section 4.2).

Hepatic impairment

In a specific study involving cirrhotic patients with chronic mild (Child-Pugh type A) or moderate (Child-Pugh type B) liver impairment, exposure to agomelatine 25 mg was substantially increased (70-times and 140-times, respectively), compared to matched volunteers (age, weight and smoking habit) with no liver failure (see section 4.2, 4.3 and 4.4).

Elderly

In a pharmacokinetic study in elderly patients (≥ 65 years), it was showed that at a dose of 25 mg the mean AUC and mean Cmax were about 4-fold and 13-fold higher for patients ≥ 75 years old compared

to patients < 75 years old. The total number of patients receiving 50 mg was too low to draw any conclusions. No dose adaptation is required in elderly patients.

Ethnic groups
There is no data on the influence of race on agomelatine pharmacokinetics.

5.3 Preclinical safety data

In mice, rats and monkeys sedative effects were observed after single and repeated administration at high doses.
In rodents, a marked induction of CYP2B and a moderate induction of CYP1A and CYP3A were seen from 125 mg/kg/day whereas in monkeys the induction was slight for CYP2B and CYP3A at 375 mg/kg/day. No hepatotoxicity was observed in rodents and monkeys in the repeat dose toxicity studies.
Agomelatine passes into the placenta and foetuses of pregnant rats.
Reproduction studies in the rat and the rabbit showed no effect of agomelatine on fertility, embryofoetal development and pre- and post-natal development.
A battery of *in vitro* and *in vivo* standard genotoxicity assays concludes to no mutagenic or clastogenic potential of agomelatine.

In carcinogenicity studies agomelatine induced an increase in the incidence of liver tumours in the rat and the mouse**,** at a dose at least 110-fold higher than the therapeutic dose. Liver tumours are most likely related to enzyme induction specific to rodents. The frequency of benign mammary fibroadenomas observed in the rat was increased with high exposures (60-fold the exposure at the therapeutic dose) but remains in the range of that of controls.

Safety pharmacology studies showed no effect of agomelatine on hERG (human Ether à-go-go Related Gene) current or on dog Purkinje cells action potential. Agomelatine did not show proconvulsive properties at ip doses up to 128 mg/kg in mice and rats.

No effect of agomelatine on juvenile animals behavioural performances, visual and reproductive function were observed. There were mild non dose dependent decreases in body weight related to the pharmacological properties and some minor effects on male reproductive tract without any impairment on reproductive performances.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Silicified microcrystalline cellulose
Mannitol
Povidone 30
Silica, colloidal anhydrous
Crospovidone
Sodium stearyl fumarate
Magnesium stearate
Stearic acid

Film-coating
Hypromellose

Macrogol
Titanium dioxide (E 171)
Talc
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

OPA/Alu/PVC/Alu blister
Pack size:
7, 14, 28, 42, 56, 84, 98, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

betapharm Arzneimittel GmbH
Kobelweg 95
86156 Augsburg
Duitsland

8 MARKETING AUTHORISATION NUMBER(S)

RVG 122588

9 DATE OF THE FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

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