Package Insert

Agrylin® capsules 0.5 mg

Anagrelide (as hydrochloride)

1. NAME OF THE MEDICINAL PRODUCT

Agrylin capsules 0.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0.5 mg anagrelide (as anagrelide hydrochloride)

Excipient(s) with known effect
Each hard capsule contains lactose monohydrate (53.7 mg) and anhydrous lactose (65.8 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule
An opaque white hard capsule imprinted with S 063

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Agrylin is indicated for the reduction of elevated platelet counts in patients with essential thrombocythaemia (ET) who are intolerant to their existing therapy or for whom other therapies are not considered appropriate.

4.2 Posology and method of administration

Treatment with Agrylin should be initiated by a clinician with experience in the management of essential thrombocythaemia.

Posology
The recommended starting dosage of anagrelide is 1 mg/day, which should be administered orally in two divided doses (0.5 mg/dose).

The starting dose should be maintained for at least one week. After one week the dosage may be titrated, on an individual basis, to achieve the lowest effective dosage required to reduce and/or maintain a platelet count below 600 x 10^9/L and ideally at levels between 150 x 10^9/L and 400 x 10^9/L. The dosage increment must not exceed 0.5 mg/day in any one week and the recommended maximum single dose should not exceed 2.5 mg (see section 4.9). During clinical development dosages of 10 mg/day have been used.

The effects of treatment with anagrelide must be monitored on a regular basis (see section 4.4). Platelet counts should be performed every two days during the first week of treatment and at least weekly thereafter until a stable maintenance dose is reached. Typically, a fall in the platelet count will be observed within 14 to 21 days of starting treatment and in most patients an adequate therapeutic response will be observed and maintained at a dosage of 1 to 3 mg/day (for further information on the clinical effects refer to section 5.1).

Elderly
The observed pharmacokinetic differences between elderly and young patients with ET (see section 5.2) do not warrant using a different starting regimen or different dose titration step to achieve an individual patient optimised anagrelide regimen.

During the clinical development approximately 50% of the patients treated with anagrelide were over 60 years of age and no age specific alterations in dosage were required in these patients. However, as expected, patients in this age group had twice the incidence of serious adverse events (mainly cardiac).

Renal impairment
There are limited pharmacokinetic data for this patient population. The potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced. Doses are titrated on an individual patient basis. (see sections 4.3).

Hepatic impairment
There are limited pharmacokinetic data for this patient population. However, hepatic metabolism represents the major route of drug clearance and liver function may therefore be expected to influence this process. Therefore it is recommended that patients with moderate or severe hepatic impairment are not treated with anagrelide. The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of anagrelide in children has not been established. The experience in children is very limited; anagrelide should be used in this patient group with caution. In the absence of specific paediatric guidelines, WHO diagnostic criteria for adult diagnosis of ET are considered to be of relevance to the paediatric population. Diagnostic guidelines for essential thrombocythemia should be followed carefully and diagnosis reassessed periodically in cases of uncertainty, with effort made to distinguish from hereditary or secondary thrombocytosis, which may include genetic analysis and bone marrow biopsy.

Typically cytoreductive therapy is considered in high risk paediatric patients.

Anagrelide treatment should only be initiated when the patient shows signs of disease progression or suffers from thrombosis. If treatment is initiated, the benefits and risks of treatment with anagrelide must be monitored regularly and the need for ongoing treatment evaluated periodically.

Platelet targets are assigned on an individual patient basis by the treating physician.

Discontinuation of treatment should be considered in paediatric patients who do not have a satisfactory treatment response after approximately 3 months.

Currently available data are described in sections 4.4, 4.8, 5.1 and 5.2, but no recommendation on a posology can be made.

Method of Administration
For oral use. The capsules must be swallowed whole. Do not crush or dilute the contents in a liquid.

4.3 Contraindications

Hypersensitivity to anagrelide or any of the excipients listed in section 6.1.
Patients with moderate or severe hepatic impairment.
Patients with moderate or severe renal impairment (creatinine clearance < 50 ml/min).

4.4 Special warnings and special precautions for use

Hepatic impairment
The potential risks and benefits of anagrelide therapy in a patient with mild impairment of hepatic function should be assessed before treatment is commenced. It is not recommended in patients with elevated transaminases (>5 times the upper limit of normal) (see section 4.2 and 4.3).

Renal impairment
The potential risks and benefits of anagrelide therapy in a patient with impairment of renal function should be assessed before treatment is commenced (see section 4.2 and 4.3).

Monitoring
Therapy requires close clinical supervision of the patient which will include a full blood count (haemoglobin and white blood cell and platelet counts), assessment of liver function (ALT and AST), renal function (serum creatinine and urea) tests and electrolytes (potassium, magnesium and calcium) before anagrelide treatment is initiated and at regular intervals thereafter.

Platelets
The platelet count will increase within 4 days of stopping treatment with anagrelide and will return to pre-treatment levels within 10 to 14 days, possibly rebounding above baseline values. Therefore platelets should be monitored frequently.

Cardiovascular
Serious cardiovascular adverse events including cases of torsades de pointes, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure have been reported (see section 4.8).

Caution should be taken when using anagrelide in patients with known risk factors for prolongation of the QT interval, such as congenital long QT syndrome, a known history of acquired QTc prolongation, medicinal products that can prolong QTc interval and hypokalaemia.

Care should also be taken in populations that may have a higher maximum plasma concentration (C_{max}) of anagrelide or its active metabolite, 3-hydroxy-anagrelide, e.g. hepatic impairment or use with CYP1A2 inhibitors (see section 4.5).

Close monitoring for an effect on the QTc interval is advisable.

A pre-treatment cardiovascular examination including a baseline ECG and echocardiography is recommended for all patients prior to initiating therapy with anagrelide. All patients should be monitored regularly during treatment (e.g. ECG or echocardiography) for evidence of cardiovascular effects that may require further cardiovascular examination and investigation. Hypokalaemia or hypomagnesaemia must be corrected prior to anagrelide administration and should be monitored periodically during therapy.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic and chronotropic effects, anagrelide should be used with caution in patients of any age with known or suspected heart disease. Moreover, serious cardiovascular adverse events have also occurred in patients without suspected heart disease and with normal pre-treatment cardiovascular examination.

Anagrelide should only be used if the potential benefits of therapy outweigh the potential risks.

Pulmonary hypertension
Cases of pulmonary hypertension have been reported in patients treated with anagrelide.
Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during anagrelide therapy.

Paediatric population
Very limited data are available on the use of anagrelide in the paediatric population and anagrelide should be used in this patient group with caution (see sections 4.2, 4.8, 5.1 and 5.2).

As with the adult population, a full blood count and assessment of cardiac, hepatic and renal function should be undertaken before treatment and regularly during treatment. The disease may progress to myelofibrosis or AML. Although the rate of such progression is not known, children have a longer disease course and may, therefore, be at increased risk for malignant transformation, relative to adults. Children should be monitored regularly for disease progression according to standard clinical practices, such as physical examination, assessment of relevant disease markers and bone marrow biopsy.

Any abnormalities should be evaluated promptly and appropriate measures taken, which may also include dose reduction, interruption or discontinuation.

Clinically relevant interactions
Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE III). Concomitant use of anagrelide with other PDE III inhibitors such as milrinone, amrinone, enoximone, olprinone and cilostazol is not recommended.

Use of concomitant anagrelide and acetylsalicylic acid has been associated with major haemorrhagic events (see section 4.5).

Thrombotic Risk
Abrupt treatment discontinuation or substantial reduction of anagrelide's dose should be avoided due to the risk of sudden increase in platelet counts, which may lead to potentially fatal thrombotic complications, such as cerebral infarction (see section 4.2). Patients should be advised how to recognize early signs and symptoms suggestive of thrombotic complications, such as cerebral infarction, and if symptoms occur to seek medical assistance.

Treatment discontinuation
In the event of dosage interruption or treatment withdrawal, the rebound in platelet count is variable, but the platelet count will start to increase within 4 days of stopping treatment with anagrelide and will return to pre-treatment levels within 10 to 14 days, possibly rebounding above baseline values. Therefore, platelets should be monitored frequently (see section 4.2).

Excipients
Agrylin contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Limited pharmacokinetic and/or pharmacodynamic studies investigating possible interactions between anagrelide and other drugs have been conducted.

Effects of other active substances on anagrelide
- *In vivo* interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

CYP1A2 inhibitors
- Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and enoxacin, and such medicinal products could theoretically adversely influence the clearance of anagrelide.

CYP inducers
- CYP1A2 inducers (such as omeprazole) could decrease the exposure of anagrelide increasing its main active metabolite. The consequences on the safety and efficacy profile of anagrelide are not established. Therefore, clinical and biological monitoring is recommended in patients taking concomitant CYP1A2 inducers. If needed, anagrelide dose adjustment could be made.

Effects of anagrelide on other substances
- Anagrelide demonstrates some limited inhibitory activity towards CYP1A2 which may present a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism e.g. theophylline.
- Anagrelide is an inhibitor of PDE III. The effects of medicinal products with similar properties such as the inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide.
- *In vivo* interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of digoxin or warfarin.
- At the doses recommended for use in the treatment of essential thrombocythaemia, anagrelide may potentiate the effects of other medicinal products that inhibit or modify platelet function e.g. acetylsalicylic acid.
- A clinical interaction study performed in healthy subjects showed that co-administration of repeat-dose anagrelide 1 mg once daily and acetylsalicylic acid 75 mg once daily may enhance the anti-platelet aggregation effects of each drug compared with administration of acetylsalicylic acid alone. In some ET patients concomitantly treated by acetylsalicylic acid and anagrelide, major haemorrhages occurred. Therefore, the potential risks of the concomitant use of anagrelide with acetylsalicylic acid should be assessed, particularly in patients with a high risk profile for haemorrhage before treatment is initiated.
- Anagrelide may cause intestinal disturbance in some patients and compromise the absorption of hormonal oral contraceptives.

Food interactions
- Food delays the absorption of anagrelide, but does not significantly alter systemic exposure.
- The effects of food on bioavailability are not considered clinically relevant to the use of anagrelide.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women of child-bearing potential should use adequate birth-control measures during treatment with anagrelide.

Pregnancy
There are no adequate data from the use of anagrelide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore Agrylin is not recommended during pregnancy.

If anagrelide is used during pregnancy, or if the patient becomes pregnant while using the medicinal product, she should be advised of the potential risk to the foetus.

Breast-feeding
It is not known whether anagrelide/metabolites are excreted in milk. Available data in animals have shown excretion of anagrelide/metabolites in milk. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during the treatment with anagrelide.

Fertility
No human data on the effect of anagrelide on fertility are available. In male rats, there was no effect on fertility or reproductive performance with anagrelide. In female rats, using doses in excess of the therapeutic range, anagrelide disrupted implantation (see section 5.3).

4.7 Effects on ability to drive and use machines

In clinical development, dizziness was commonly reported. Patients are advised not to drive or operate machinery while taking Agrylin if dizziness is experienced.

4.8 Undesirable effects

Summary of the safety profile
The safety of anagrelide has been examined in 4 open-label clinical studies. In 3 of the studies 942 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In these studies 22 patients received anagrelide for up to 4 years.

In the later study 3660 patients who received anagrelide at a mean dose of approximately 2 mg/day were assessed for safety. In this study 34 patients received anagrelide for up to 5 years.

The most commonly reported drug-related adverse reactions were headache occurring at approximately 14%, palpitations occurring at approximately 9%, fluid retention and nausea both occurring at approximately 6%, and diarrhoea occurring at 5%. These adverse drug reactions are expected based on the pharmacology of anagrelide (inhibition of PDE III). Gradual dose titration may help diminish these effects (see section 4.2).

Tabulated list of adverse reactions
Adverse reactions arising from clinical studies, post-authorisation safety studies and spontaneous reports are presented in the table below. Within the system organ classes they are listed under the following headings: 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Frequency of adverse reactions **Italic text denotes post-marketing adverse reactions*				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Blood and lymphatic system disorders		Anaemia	Pancytopenia Thrombocytopenia Haemorrhage Ecchymosis		
Metabolism and nutrition disorders		Fluid retention	Oedema Weight loss	Weight gain	
Nervous system disorders	Headache	Dizziness	Depression Amnesia Confusional state Insomnia Paraesthesia Hypoaesthesia Nervousness Dry mouth	Migraine Dysarthria Somnolence Abnormal coordination	Cerebral infarction
Eye disorders				Diplopia Vision impairment	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Tachycardia Palpitations	Ventricular tachycardia Cardiac failure congestive Atrial fibrillation Supraventricular tachycardia Arrhythmia Hypertension Syncope	Myocardial infarction Cardiomyopathy Cardiomegaly Pericardial effusion Angina pectoris Orthostatic hypotension Vasodilatation	**Torsade de pointes* **Prinzmetal angina*

MedDRA System Organ Class	Frequency of adverse reactions *Italic text denotes post-marketing adverse reactions*				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Respiratory, thoracic and mediastinal disorders			Pulmonary hypertension Pneumonia Pleural effusion Dyspnoea Epistaxis	Lung infiltration	**Interstitial lung disease including pneumonitis and allergic alveolitis*
Gastrointestinal disorders		Diarrhoea Vomiting Abdominal pain Nausea Flatulence	Gastrointestinal haemorrhage Pancreatitis Decreased appetite Dyspepsia Constipation Gastrointestinal disorder	Colitis Gastritis Gingival bleeding	
Hepatobiliary disorders			Hepatic enzymes increased		**Hepatitis*
Skin and subcutaneous tissue disorders		Rash	Alopecia Pruritus Skin discoloration	Dry skin	
Musculoskeletal and connective tissue disorders			Arthralgia Myalgia Back pain		
Renal and urinary disorders			Impotence	Renal failure Nocturia	**Tubulointerstitial nephritis*
General disorders and administration site conditions		Fatigue	Chest pain Fever Chills Malaise Weakness	Influenza-like illness Pain Asthenia	
Investigations				Blood creatinine increased	

Paediatric population
48 patients aged 6-17 years (19 children and 29 adolescents) have received anagrelide for up to 6.5 years either in clinical studies or as part of a disease registry (see section 5.1).
The majority of adverse events observed were among those listed in the package insert. However, safety data are limited and do not allow a meaningful comparison between adult and paediatric patients to be made (see section 4.4).

4.9 Overdose
Post-marketing case reports of intentional overdose with anagrelide have been received. Reported symptoms include sinus tachycardia and vomiting. Symptoms resolved with conservative management.

Agrylin, at higher than recommended doses, has been shown to produce reductions in blood pressure with occasional instances of hypotension. A single 5 mg dose of anagrelide can lead to a fall in blood pressure usually accompanied by dizziness.

A specific antidote for anagrelide has not been identified. In case of overdose, close clinical supervision of the patient is required; this includes monitoring of the platelet count for thrombocytopenia. Dosage should be decreased or stopped, as appropriate, until the platelet count returns to within the normal range.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other neoplastic agents, ATC Code: L01XX35

Mechanism of action
The precise mechanism by which anagrelide reduces blood platelet count is unknown. In cell culture studies, anagrelide suppressed expression of transcription factors including GATA-1 and FOG-1 required for megakaryocytopoiesis, ultimately leading to reduced platelet production.

In vitro studies of human megakaryocytopoiesis established that anagrelide's inhibitory actions on platelet formation in man are mediated via retardation of maturation of megakaryocytes, and reducing their size and ploidy. Evidence of similar *in vivo* actions was observed in bone marrow biopsy samples from treated patients.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III.

Clinical efficacy and safety
The safety and efficacy of anagrelide as a platelet lowering agent have been evaluated in four open-label, non-controlled clinical trials (study numbers 700-012, 700-014, 700-999 and 13970-301) including more than 4000 patients with myeloproliferative neoplasms (MPNs). In patients with essential thrombocythaemia complete response was defined as a decrease in platelet count to ≤600 x 10^9/L or a ≥50% reduction from baseline and maintenance of the reduction for at least 4 weeks. In studies 700-012, 700-014, 700-999 and study 13970-301 the time to complete response ranged from 4 to 12 weeks. Clinical benefit in terms of thrombohaemorrhagic events has not been convincingly demonstrated.

Effects on Heart Rate and QTc Interval
The effect of two dose levels of anagrelide (0.5 mg and 2.5 mg single doses) on the heart rate and QTc interval was evaluated in a double-blind, randomised, placebo- and active-controlled, cross-over study in healthy adult men and women.

A dose-related increase in heart rate was observed during the first 12 hours, with the maximum increase occurring around the time of maximal concentrations. The maximum change in mean heart rate occurred at 2 hours after administration and was +7.8 beats per minute (bpm) for 0.5 mg and +29.1 bpm for 2.5 mg.

A transient increase in mean QTc was observed for both doses during periods of increasing heart rate and the maximum change in mean QTcF (Fridericia correction) was +5.0 msec occurring at 2 hours for 0.5 mg and +10.0 msec occurring at 1 hour for 2.5 mg.

Paediatric population
In an open-label clinical study in 8 children and 10 adolescents (including patients who were anagrelide treatment naïve or who had been receiving anagrelide for up to 5 years pre-study), median platelet counts were decreased to controlled levels after 12 weeks of treatment. The average daily dose tended to be higher in adolescents.

In a paediatric registry study, median platelet counts were reduced from diagnosis and maintained for up to 18 months in 14 paediatric ET patients (4 children, 10 adolescents) with anagrelide treatment. In earlier, open-label studies, median platelet count reductions were observed in 7 children and 9 adolescents treated for between 3 months and 6.5 years.

The safety and efficacy of anagrelide in children has not been established and no recommendation on a posology can be made. Across all studies in paediatric ET patients, the average total daily dose of anagrelide was highly variable, but overall the data suggest that adolescents could follow similar starting and maintenance doses to adults and that a lower starting dose of 0.5 mg/day would be more appropriate for children over 6 years (see sections 4.2, 4.4, 4.8, 5.2). In all paediatric patients, careful titration to a patient-specific daily dose is needed.

5.2 Pharmacokinetic properties
Absorption
Following oral administration of anagrelide in man, at least 70% is absorbed from the gastrointestinal tract. In fasted subjects, peak plasma levels occur about 1 hour after administration. Pharmacokinetic data from healthy subjects established that food decreases the C_{max} of anagrelide by 14%, but increases the AUC by 20%. Food had a more significant effect on the active metabolite and decreased the C_{max} by 29%, although it had no effect on the AUC.

Biotransformation
Anagrelide is primarily metabolised by CYP1A2 to form, 3-hydroxy anagrelide, which is further metabolized via CYP1A2 to the inactive metabolite, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline.

Elimination
The plasma half-life of anagrelide is short, approximately 1.3 hours and as expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Less than 1% is recovered in the urine as anagrelide. The mean recovery of 2 amino-5, 6-dichloro-3, 4-dihydroquinazoline in urine is approximately 18-35% of the administered dose.

Additionally, these results show no evidence of auto-induction of anagrelide clearance.

Linearity
Dose proportionality has been found in the dose range 0.5 mg to 2 mg.

Paediatric population
Pharmacokinetic data from exposed fasting children and adolescents (age range 7-16 years) with essential thrombocythaemia indicate that dose and body weight normalised exposure, C_{max} and AUC, of anagrelide were lower in children/adolescents compared to adults. There was also a trend to higher dose-normalised exposure to the active metabolite.

Elderly
Pharmacokinetic data from fasting elderly patients with ET (age range 65-75 years) compared to fasting adult patients (age range 22-50 years) indicate that the C_{max} and AUC of anagrelide were 36% and 61% higher respectively in elderly patients, but that the C_{max} and AUC of the active metabolite, 3-hydroxy anagrelide, were 42% and 37% lower respectively in the elderly patients. These differences were likely to be caused by lower presystemic metabolism of anagrelide to 3-hydroxy anagrelide in the elderly patients.

5.3 Preclinical safety data
Repeated dose toxicity
Following repeated oral administration of anagrelide in dogs, subendocardial haemorrhage and focal myocardial necrosis was observed at 1 mg/kg/day or higher in males and females with males being more sensitive. The no observed effect level (NOEL) for male dogs (0.3 mg/kg/day) corresponds to 0.1, 0.1, and 1.6-fold the AUC in humans for anagrelide at 2 mg/day, and the metabolites BCH24426 and RL603, respectively.

Reproductive toxicity
Fertility
In male rats, anagrelide at oral doses up to 240 mg/kg/day (>1000 times a 2 mg/day dose, based on body surface area) was found to have no effect on fertility and reproductive performance. In female rats increases in pre- and post-implantation losses and a decrease in the mean number of live embryos was observed at 30 mg/kg/day. The NOEL (10 mg/kg/day) to this effect was 143, 12 and 11-fold higher than the AUC in humans administered a dose of anagrelide 2 mg/day, and the metabolites BCH24426 and RL603, respectively.

Embryofoetal developmental studies
Maternally toxic dosages of anagrelide in rats and rabbits were associated with increased embryo resorption and foetal mortality.
In a pre- and post-natal development study in female rats, anagrelide at oral doses of ≥10 mg/kg produced a non-adverse increase in gestational duration. At the NOEL dose (3 mg/kg/day), the AUCs for anagrelide and the metabolites BCH24426 and RL603 were 14, 2 and 2-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day.

Anagrelide at ≥60 mg/kg increased parturition time and mortality in the dam and foetus respectively. At the NOEL dose (30 mg/kg/day), the AUCs for anagrelide and the metabolites BCH24426 and RL603 were 425-, 31- and 13-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day, respectively.

Mutagenic and carcinogenic potential
Studies on the genotoxic potential of anagrelide did not identify any mutagenic or clastogenic effects.

In a two year rat carcinogenicity study, non-neoplastic and neoplastic findings were observed and related or attributed to an exaggerated pharmacological effect. Among them, the incidence of adrenal phaeochromocytomas was increased relative to controls in males at all dose levels (≥ 3 mg/kg/day) and in females receiving 10 mg/kg/day and above. The lowest dose in males (3 mg/kg/day) corresponds to 37 times the human AUC exposure after a 1 mg twice daily dose. Uterine adenocarcinomas, of epigenetic origin, could be related to an enzyme induction of CYP1 family. They were observed in females receiving 30 mg/kg/day, corresponding to 572 times the human AUC exposure after a 1 mg twice daily dose.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients

Capsule contents
Povidone (E1201)
Lactose, anhydrous
Lactose monohydrate
Cellulose, microcrystalline (E460)
Crospovidone
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Dehydrated alcohol
Isopropyl alcohol
Butyl alcohol
Propylene glycol
Strong ammonium solution
Potassium hydroxide (E525)
Black iron oxide (E172)
Water

6.2 Incompatibilities
Not applicable

6.3 Recommended storage condition
Store between 15°C and 25°C.

6.4 Nature and contents of container
HDPE bottles containing desiccant with child-resistant closures containing 100 capsules

6.5 Special precautions for disposal
No special requirements

7. MANUFACTURER
Patheon Manufacturing Services LLC,
Greenville, NC 27834, USA

8. DATE OF TEXT
July 2022