

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

AGRYLIN® 0.5 mg hard capsules

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 lactose (65.8 mg).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Opaque white capsule containing white powder; printed with Shire logo 'S' on the cap and '063' on the body in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AGRYLIN capsules are indicated for the treatment of essential thrombocythaemia (ET).

4.2 Dose and method of administration

Adults and Elderly

The recommended starting dose of AGRYLIN is 0.5 mg twice daily. The starting dose should be maintained for at least one week. After one week, the dose may be titrated on an individual basis, to achieve the lowest effective dose required to reduce and/or maintain a platelet count below $600 \times 10^9/L$. The dose increment must not exceed more than 0.5 mg/day in any one week. Dosage should not exceed 10 mg per day or 2.5 mg in a single dose.

Paediatrics

There are limited data on the appropriate starting dose for paediatric patients. Starting doses in paediatric patients have ranged from 0.5 mg per day to 0.5 mg four times daily, so an initial dose of 0.5 mg per day is recommended. The starting dose should be maintained for at least one week. After one week the dose may be titrated, on an individual basis. Platelet targets are assigned on an individual patient basis by the treating physician. The dose increment must not exceed 10 mg per day or 2.5 mg in a single dose. Discontinuation of treatment should be considered in paediatric patients who do not have a satisfactory treatment response after approximately 3 months (see 4.4 Special warnings and precautions for use).

Hepatic Impairment

It is recommended that patients with moderate hepatic impairment start AGRYLIN therapy at a dose of 0.5 mg/day (see Section 5.2: Special Populations Pharmacokinetics).

Renal Impairment

No dosage adjustment is required (see Section 5.2: Special Populations Pharmacokinetics)

Patient Monitoring

The effects of treatment with anagrelide must be monitored on a regular basis (see Section 4.4: Special Warnings and Precautions for Use). If the starting dose is > 1 mg per day, 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 7 to 21 days of starting treatment and in most patients an adequate therapeutic response will be observed and maintained at a dose of 1 to 3 mg per day. In the event of dosage

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interruption or treatment withdrawal, the rebound in platelet count is variable, but platelet counts typically will start to rise within 4 days and return to baseline levels in one to two weeks, possibly rebounding above baseline values. Therefore, platelet count should be monitored frequently (see 4.4 Special warnings and precautions for use).

4.3 Contraindications

AGRYLIN is contraindicated in patients who have developed hypersensitivity to anagrelide hydrochloride or any of its excipients (see Section 6.1: List of Excipients) and in patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take AGRYLIN as it contains lactose.

Cardiovascular

Due to anagrelide's positive inotropic and chronotropic effects, anagrelide should be used with caution in patients with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks.

A pre-treatment cardiovascular examination (including investigations such as echocardiography, electrocardiogram) is recommended for all patients. Patients should be monitored during treatment for cardiovascular effects and further investigations carried out as necessary.

Anagrelide has been shown to increase the heart rate, resulting in an apparent increase in QTc interval of the electrocardiogram in healthy volunteers. The clinical impact of this effect is unknown (see Section 5.1: Pharmacodynamic Properties).

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: Interactions with Other Medicines].

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.

Bleeding

Use of concomitant anagrelide and acetylsalicylic acid has been associated with major haemorrhagic events (see Section 4.5: Interactions with Other Medicines).

Hepatic Impairment

The potential risks and benefits of anagrelide therapy in a patient with mild to moderate hepatic impairment should be assessed before and during treatment (see Section 4.2: Dose and Method of Administration, and Section 5.2: Special Populations Pharmacokinetics).

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Renal Impairment

Patients with renal impairment (serum creatinine ≥ 0.18 mmol/L) should be monitored closely since they are at greater risk of renal toxicity while receiving anagrelide (see Section 4.8: Undesirable Effects, Renal and urinary disorders).

Laboratory Monitoring

Therapy requires close clinical supervision of the patient which will include a full blood count (haemoglobin, white blood cell and platelet counts) and assessment of liver function (ALT and AST), renal function (serum creatinine and urea) and electrolytes (potassium, magnesium and calcium).

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 4.2 Dose and method of administration). Patients should be advised how to recognise early signs and symptoms suggestive of thrombotic complications, such as cerebral infarction, and if symptoms occur to seek medical assistance.

Therapeutic doses of anagrelide may cause cardiovascular effects, including vasodilation, tachycardia, palpitations and congestive cardiac failure. A pre-treatment cardiovascular examination (including investigations such as echocardiography, electrocardiogram) is recommended for all patients. Hypokalaemia or hypomagnesaemia must be corrected prior to anagrelide administration. Anagrelide should be used with caution in patients with known or suspected heart disease or at high risk of vascular events, and only if the potential benefits of therapy outweigh the potential risks (see also Patient Monitoring).

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. 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 and use of an alternative treatment considered.

Paediatric Patients

The efficacy and safety of anagrelide in patients under the age of 16 years have not been established. Experience with anagrelide in paediatric patients was based on an open-label safety and PK/PD study conducted in 18 paediatric patients aged 7 to 16 years with thrombocytopenia secondary to essential thrombocythemia (ET). There were no apparent trends or differences in the types of adverse events observed between paediatric patients compared to those of the adult patients.

Elderly Patients

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

Treatment discontinuation

In the event of dosage interruption or treatment withdrawal, the rebound 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 Dose and method of administration).

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4.5 Interaction with other medicines and other forms of interaction

Effects of Anagrelide on Other Medicines

Other PDE3 Inhibitors

Anagrelide is an inhibitor of PDE3. The effects of medicinal products with similar properties such as inotropes milrinone, enoximone, amrinone, olprinone and cilostazol may be exacerbated by anagrelide.

Medicines that Increase Bleeding Risk

At therapeutic doses, anagrelide may potentiate the effects of other medicinal products that inhibit platelet aggregation.

Acetylsalicylic Acid (Aspirin)

In some patients with essential thrombocythemia (ET) concomitantly treated by acetylsalicylic acid and anagrelide, major haemorrhages occurred; therefore, the potential risks of the concomitant use of these medicines should be assessed, particularly in patients with a high-risk profile for haemorrhage before treatment is initiated.

In two clinical interaction studies in healthy subjects, co-administration of a single-dose anagrelide 1 mg once daily and acetylsalicylic acid (aspirin) 900 mg or repeated dose anagrelide 1 mg once daily and aspirin 75 mg once daily, showed greater ex-vivo anti-platelet aggregation effects than administration of aspirin alone.

Warfarin

In vivo interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of warfarin.

Medicines Metabolised by CYP1A2

Anagrelide demonstrates some limited inhibitory activity towards CYP1A2 which may present a theoretical potential for interaction with other co-administered medicines that are substrate of the same metabolic enzyme system.

Digoxin

In vivo interaction studies in humans have demonstrated that anagrelide does not affect the pharmacokinetic properties of digoxin.

Effects of Other Substances on Anagrelide

CYP1A2 Inhibitors

Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and ciprofloxacin, and such medicinal products could theoretically adversely influence the clearance of anagrelide, thereby increasing plasma concentrations. Anagrelide demonstrated inhibitory activity towards CYP1A2 in vitro, which presents a theoretical potential for interaction with other co-administered medicinal products sharing that clearance mechanism (e.g. theophylline).

CYP1A2 Inducers

CYP1A2 inducers could decrease the exposure of anagrelide. Patients taking concomitant CYP1A2

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inducers (e.g., omeprazole) may need to have their dose titrated to compensate for the decrease in anagrelide exposure.

Digoxin or Warfarin

In vivo interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

Preclinical data indicate an augmented anticoagulant effect when heparin and anagrelide were used in combination

4.6 Fertility, pregnancy and lactation

Effects on Fertility

No human data on the effect of anagrelide on fertility are available. Studies in animals have shown reproductive toxicity. 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.

Use in Pregnancy (Category B3)

Use of anagrelide is not recommended during pregnancy. Women of child-bearing potential should use adequate birth-control measures during treatment with anagrelide.

Use in Lactation

Excretion of anagrelide-related material into milk has been demonstrated in rats. Because of the potential for adverse reactions in breast-feeding infants, a decision should be made whether to discontinue breast-feeding or to discontinue the medicine, taking into account the importance of the medicine to the mother.

4.7 Effects on ability to drive and use machines

AGRYLIN may cause dizziness in some patients. Caution should be shown when driving or operating machinery whilst on treatment with AGRYLIN.

4.8 Undesirable effects

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 adverse reactions associated with anagrelide 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 medicine reactions are expected based on the pharmacology of anagrelide. Gradual dose titration may help diminish these effects.

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 ($\geq 1/10$); 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

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from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse Drug Reactions Associated with AGRYLIN

**Italic text denotes post-marketing ADRs*

MedDRA System Organ Class	<i>Frequency of adverse reactions</i>				
	<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Not known</i>
<i>Blood and lymphatic system disorders</i>		Anaemia	Thrombocytopenia		
<i>Metabolism and nutrition disorders</i>			Decreased appetite		
<i>Nervous system disorders</i>	Headache	Dizziness Hypoesthesia	Syncope Amnesia Paresthesia	Migraine Somnolence	Cerebral infarction
<i>Psychiatric disorders</i>			Depression Confusional state Insomnia Nervousness		
<i>Eye disorders</i>				Diplopia Visual impairment	
<i>Ear and labyrinth disorders</i>				Tinnitus	
<i>Cardiac disorders</i>		Tachycardia Palpitations	Ventricular tachycardia Supraventricular tachycardia Congestive cardiac failure Atrial fibrillation Arrhythmia	Myocardial infarction Cardiomyopathy	<i>*Torsade de pointes Prinzmetal angina</i>
<i>Respiratory, thoracic and mediastinal disorders</i>			Pleural effusion Dyspnea Epistaxis Pulmonary hypertension	Lung infiltration	<i>*Interstitial lung disease including pneumonitis and allergic alveolitis</i>

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Adverse Drug Reactions Associated with AGRYLIN

**Italic text denotes post-marketing ADRs*

MedDRA System Organ Class	<i>Frequency of adverse reactions</i>				
	<i>Very common</i>	<i>Common</i>	<i>Uncommon</i>	<i>Rare</i>	<i>Not known</i>
<i>Gastrointestinal disorders</i>		Diarrhoea Vomiting Abdominal pain Nausea Flatulence	Gastrointestinal haemorrhage Pancreatitis Dyspepsia Constipation	Gastritis	
<i>Hepatobiliary disorders</i>					<i>*Hepatitis</i>
<i>Skin and subcutaneous tissue disorders</i>		Rash	Echymosis Alopecia Pruritus		
<i>Musculoskeletal and connective tissue disorders</i>			Arthralgia Myalgia Back pain		
<i>Renal and urinary disorders</i>				Renal failure	<i>*Tubulointerstitial nephritis</i>
<i>General disorders and administration site conditions</i>			Oedema Chest pain Fever Chills Malaise	Influenza-like illness Pain Asthenia	
<i>Vascular disorders</i>			Haemorrhage Hypertension	Orthostatic hypotension Vasodilatation	
<i>Infections and infestations</i>			Pneumonia		
<i>Investigations</i>			Hepatic enzymes increased		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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4.9 Overdose

Acute Signs and Symptoms

At higher than recommended doses, anagrelide has been shown to cause reductions in blood pressure, with occasional hypotension. In post-marketing reports of intentional overdose with anagrelide, symptoms included sinus tachycardia and vomiting. Symptoms resolved with supportive management.

Platelet reduction from anagrelide therapy is dose-related; therefore thrombocytopenia, which can potentially cause bleeding, is expected from overdosage.

Management and Treatment

Close clinical supervision of the patient is required; this especially includes monitoring of the platelet count for thrombocytopenia. If a patient develops thrombocytopenia, dosage should be decreased or stopped until the platelet count returns to within the normal range. Further management should be instituted as clinically indicated.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

Pharmacodynamic Effects

In blood withdrawn from normal volunteers treated with anagrelide, a disruption was found in the postmitotic phase of megakaryocyte development and a reduction in megakaryocyte size and ploidy. At therapeutic doses, anagrelide does not produce significant changes in white cell counts or coagulation parameters, and may have a small, but clinically insignificant effect on red cell parameters. The active metabolite, 3-hydroxy anagrelide, has similar potency and efficacy to that of anagrelide in the platelet lowering effect; however, exposure (measured by plasma AUC) to 3-hydroxy anagrelide is approximately 2-fold higher compared to anagrelide.

Anagrelide and 3-hydroxy anagrelide inhibit cyclic AMP phosphodiesterase 3 (PDE3) and 3-hydroxy anagrelide is approximately forty times more potent than anagrelide (IC₅₀s = 0.9 and 36 nM, respectively). PDE3 inhibition does not alter platelet production. PDE3 inhibitors, as a class can inhibit platelet aggregation. However, significant inhibition of platelet aggregation is observed only at doses of anagrelide higher than those typically required to reduce platelet count. PDE3 inhibitors have cardiovascular (CV) effects including vasodilation, positive inotropy and chronotropy.

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 60 healthy adult men and women.

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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.

An apparent 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 (upper 2-sided 90% CI 8.0 msec) occurring at 2 hours for 0.5 mg and +10.0 msec (upper 2-sided 90% CI 12.7 msec) occurring at 1 hour for 2.5 mg. The evidence suggests that this increase in QTc may be due to the physiological effect of the increase heart rate and the corresponding QT-RR hysteresis, rather than a direct effect on repolarization. Anagrelide exposure was higher in women than men (C_{max} 55 - 75% higher; AUC 90% higher) and women had higher heart rate changes (and QTc changes) than men around the time of T_{max} .

The recommended starting dosage of AGRYLIN is 0.5 mg twice daily and should be increased by not more than 0.5 mg/day in any one week (see Section 4.2: Dose and Method of Administration).

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 also decreased the C_{max} of the active metabolite, 3- hydroxy anagrelide, by 29%, although it had no effect on the AUC.

Metabolism

Anagrelide is primarily metabolised by CYP1A2 to form 3-hydroxy anagrelide, which is further metabolised via CYP1A2 to the inactive metabolite.

Elimination

The plasma half-life of anagrelide is short, approximately 1.5 hours and as expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Less than 1% of the administered dose is recovered in the urine as anagrelide and approximately 3% and 16 - 20% of the administered dose is recovered as 3-hydroxy anagrelide and RL603, respectively.

Special Populations Pharmacokinetics

Paediatrics

Pharmacokinetic data from exposed fasting children and adolescents (age range – 7 through 16 years) with essential thrombocythemia (ET) indicate that dose normalised exposure, C_{max} and AUC, of anagrelide tended to be higher in children/adolescents compared with adults. There was also a trend to higher dose-normalised exposure to the active metabolite.

Geriatrics

Pharmacokinetic data from fasting elderly patients with ET (age range 65 through 75 years) compared to fasting adult patients (age range 22 through 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 pre-systemic metabolism of anagrelide to 3-hydroxy anagrelide in the elderly patients.

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Hepatic Impairment

Hepatic metabolism represents the major route of anagrelide clearance. Anagrelide has not been studied in patients with severe hepatic impairment. A pharmacokinetic study at a single dose of 1 mg anagrelide in subjects with moderate hepatic impairment (Child Pugh score 7-9) showed a 2-fold increase in mean anagrelide C_{max} and an 8-fold increase in mean anagrelide AUC compared to healthy subjects. Additionally, subjects with moderate hepatic impairment showed 24% lower mean 3-hydroxy anagrelide C_{max} and 77% higher mean 3-hydroxy anagrelide AUC compared to healthy subjects.

Renal Impairment

A pharmacokinetic study at a single dose of 1 mg anagrelide in subjects with severe renal impairment (creatinine clearance <30 mL/min) showed no significant effects on the pharmacokinetics of anagrelide. Exposure ($AUC_{0-\infty}$) to the active metabolite of anagrelide, 3-hydroxy anagrelide, was approximately 50% higher in renally impaired subjects; however, maximum observed plasma concentrations did not differ between the study groups.

5.3 Preclinical safety data

Reproductive Toxicology

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 no observed effect level (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 3-hydroxy anagrelide and RL603, respectively.

Embryofetal Development Studies

Maternally toxic doses of anagrelide in rats and rabbits were associated with increased embryo resorption and fetal 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 3-hydroxy anagrelide 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 fetus respectively. At the NOEL dose (30mg/kg/day), the AUCs for anagrelide and the metabolites 3-hydroxy anagrelide and RL603 were 425-, 31- and 13-fold higher than the AUC in humans administered an oral dose of anagrelide 2 mg/day, respectively.

In a placental transfer study, a single oral dose of [^{14}C] anagrelide hydrochloride was administered to pregnant rats on gestation Day 17. Medicine-related radioactivity was detected in maternal and fetal tissue.

Lactation

In rats given a single oral dose of [^{14}C] anagrelide hydrochloride, medicine related material was detected in the milk, with milk to maternal plasma concentration ratios of up to 3.5 observed.

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Carcinogenicity/Mutagenesis

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

In a two year rat carcinogenicity study, non-neoplastic findings were observed and related or attributed to an exaggerated pharmacological effect. Among them, the incidence of adrenal pheochromocytomas was increased relative to control 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

- Crospovidone
- Lactose
- Lactose monohydrate
- Magnesium stearate
- Microcrystalline cellulose
- Povidone
- Gelatin
- Titanium dioxide
- TekPrint SW-9008 Black Ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

AGRYLIN capsules are packaged as 100 capsules in HDPE bottles with a polypropylene child resistant cap, a desiccant and cotton coil.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine

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8 SPONSOR

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9 DATE OF FIRST APPROVAL

04 April 2019

10 DATE OF REVISION OF THE TEXT

12 August 2022

SUMMARY TABLE OF CHANGES

<u>Section changed</u>	<u>Summary of changes</u>
4.4	New subsection added: 'Treatment discontinuation' Added statement under 'Thrombotic risk'
4.5	Added statement added under 'CYP1A2 Inhibitors'
4.6	Added statement under 'Effects on fertility'
4.8	New ADR under 'Nervous System disorders'

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