ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xagrid 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 anhydrous lactose (65.8 mg).

For the 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

Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy.

An at risk patient
An at risk essential thrombocythaemia patient is defined by one or more of the following features:

- > 60 years of age or
- a platelet count > 1000 x 10^9/l or
- a history of thrombo-haemorrhagic events.

4.2 Posology and method of administration

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

The recommended starting dose 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 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 x 10^9/l and ideally at levels between 150 x 10^9/l and 400 x 10^9/l. The dose increment must not exceed more than 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 doses of 10 mg/day have been used.

The effects of treatment with anagrelide must be monitored on a regular basis (see section 4.4). If the starting dose is > 1 mg/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 14 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/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 clinical development approximately 50% of the patients treated with anagrelide were over 60 years of age and no age specific alterations in dose 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.

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 experience in children is limited; anagrelide should be used in this patient group with caution. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

4.3 Contraindications

Hypersensitivity to anagrelide or to 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 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 sections 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 sections 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), and assessment of liver function (ALT and AST) and renal function (serum creatinine and urea) tests.

Platelets
The platelet count will increase within 4 days of stopping treatment with Xagrid capsules and will return to pre-treatment levels within 10 to 14 days.

Cardiovascular
Serious cardiovascular adverse events including cases of cardiomyopathy, cardiomegaly, congestive heart failure and cardiac arrhythmias have been reported (see section 4.8).

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.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

Paediatric population
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 5.1 and 5.2).

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.

Excipients
Xagrid 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 medicinal products have been conducted.

Drug interactions: effects of other substances on anagrelide
- Anagrelide is primarily metabolised by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine and omeprazole, and such medicinal products could theoretically adversely influence the clearance of anagrelide.
- *In vivo* interaction studies in humans have demonstrated that digoxin and warfarin do not affect the pharmacokinetic properties of anagrelide.

Drug interactions: 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 Xagrid is not recommended during pregnancy.

If Xagrid 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 unknown whether anagrelide hydrochloride/metabolites are excreted in milk. A risk to the newborn/infant cannot be excluded. Breast-feeding should be discontinued during treatment with Xagrid.

Fertility
There are no fertility data available on anagrelide.

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.

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

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 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 summary 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).

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
Blood and lymphatic system disorders		Anaemia	Thrombocytopenia Pancytopenia Ecchymosis Haemorrhage		
Metabolism and nutrition disorders		Fluid retention	Oedema Weight loss	Weight gain	
Nervous system disorders	Headache	Dizziness	Paraesthesia Insomnia Depression Confusion Hypoaesthesia Nervousness Dry mouth Amnesia	Somnolence Abnormal coordination Dysarthria Migraine	
Eye disorders				Vision abnormal Diplopia	
Ear and labyrinth disorders				Tinnitus	
Cardiac disorders		Palpitations Tachycardia	Congestive heart failure Hypertension Arrhythmia Atrial fibrillation Supraventricular tachycardia Ventricular tachycardia Syncope	Angina pectoris Myocardial infarction Cardiomegaly Cardiomyopathy Pericardial effusion Vasodilatation Postural hypotension	
Respiratory, thoracic and mediastinal disorders			Dyspnoea Epistaxis Pleural effusion Pneumonia	Pulmonary hypertension Pulmonary infiltrates	Allergic alveolitis, including interstitial lung disease and pneumonitis
Gastrointestinal disorders		Nausea Diarrhoea Abdominal pain Flatulence Vomiting	Dyspepsia Anorexia Pancreatitis Constipation Gastrointestinal haemorrhage Gastrointestinal disorder	Colitis Gastritis Gingival bleeding	
Hepatobiliary disorders			Hepatic enzymes increased		Hepatitis
Skin and		Rash	Alopecia	Dry skin	

MedDRA System Organ Class	Frequency of Adverse Reactions				
	Very common	*Common*	*Uncommon*	*Rare*	*Not known*
subcutaneous tissue disorders			Skin discoloration Pruritus		
Musculoskeletal and connective tissue disorders			Myalgia Arthralgia Back pain		
Renal and urinary disorders			Impotence	Nocturia Renal failure	Tubulointerstitial nephritis
General disorders and administration site conditions		Fatigue	Chest pain Weakness Chills Malaise Fever	Asthenia Pain Flu-like syndrome	
Investigations				Blood creatinine increased	

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.

Xagrid, 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. Dose 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 antineoplastic agents, ATC Code: L01XX35.

The specific mechanism of action by which anagrelide reduces platelet count is not yet fully understood although it has been confirmed that anagrelide is platelet selective from *in vitro* and *in vivo* study information.

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.

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 disorders (MPDs). In patients with essential thrombocythaemia complete response was defined as a decrease in platelet count to $\leq 600 \times 10^9$/l or a $\geq 50\%$ 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.

Paediatric population
An open label clinical study with a 3 month treatment period did not raise any safety concerns for anagrelide in 17 children/adolescent patients with ET (age range 7 - 14 years) compared to 18 adult patients. Earlier during clinical development a limited number (12) of children (age range 5 - 17 years) with essential thrombocythaemia were treated with anagrelide.

This medicinal product has been authorised under "Exceptional Circumstances".
This means that due to the rarity of this disease it has not been possible to obtain complete information on this medicine.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

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 a 0.5 mg dose; the plasma half-life is short, approximately 1.3 hours. Dose proportionality has been found in the dose range 0.5 mg to 2 mg.

Anagrelide is primarily metabolised by CYP1A2; less than 1% is recovered in the urine as anagrelide. Two major urinary metabolites, 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline and 3-hydroxy anagrelide have been identified. The mean recovery of 2-amino-5, 6-dichloro-3, 4-dihydroquinazoline in urine is approximately 18-35% of the administered dose.

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.

As expected from its half-life, there is no evidence for anagrelide accumulation in the plasma. Additionally these results show no evidence of auto-induction of the anagrelide clearance.

Paediatric population
Pharmacokinetic data from fasting children and adolescents (age range 7 - 14 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 lower exposure to the active metabolite. These observations may be a reflection of more efficient metabolic clearance in younger subjects.

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

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Repeated dose toxicity
Following repeated administration of anagrelide, at doses of 1 mg/kg/day or higher, subendocardial haemorrhage and focal myocardial necrosis occurred in dogs.

Reproductive toxicology
Maternally toxic doses of anagrelide (60 mg/kg/day and above) in rats and rabbits were associated with increased embryo resorption and foetal mortality.

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 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

Capsule contents
Povidone (E1201)
Anhydrous lactose
Lactose monohydrate
Microcrystalline cellulose (E460)
Crospovidone
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)

Printing ink
Shellac
Strong ammonium solution
Potassium hydroxide (E525)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child-resistant closures and desiccant containing 100 capsules.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Hampshire International Business Park
Chineham
Basingstoke
Hampshire RG24 8EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER

EU/1/04/295/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2004
Date of latest renewal: 16 November 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Wasdell Packaging Limited, Units 6, 7, 8 Euro Way, Blagrove, Swindon, SN5 8YW, United Kingdom.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures.

Clinical aspects:

Description	Due date
1. Shire will conduct a Post Authorisation Safety Study (PASS), Study **SPD422-401:** A non-interventional, post authorisation safety study, to continuously monitor safety and pregnancy outcomes in a cohort of at-risk Essential Thrombocythaemia (ET) subjects exposed to Xagrid compared to other conventional cytoreductive treatments. *Objectives*: *Primary* To continuously monitor safety and pregnancy outcomes in a cohort of at-risk ET subjects exposed to Xagrid compared to other conventional	Annually, as part of the annual reassessment

	cytoreductive treatments. *Secondary* *Efficacy (platelet reduction, incidence of thrombohaemorrhagic events).* *Drug utilisation (drug type, drug dose, duration of exposure).* Updates and progress reports were provided at 6 monthly intervals for 5 years post-approval on patients treated with Xagrid. Study recruitment was closed in April 2009, with a commitment to follow up all patients for 5 years to obtain specific information on safety and pregnancy outcomes. Following the 5 year review annual reports will be provided. Study recruitment was initiated during May 2005. An annual safety update report should be provided as part of the Annual Reassessement.	
2.	Shire will provide an annual update of all published data concerning the efficacy and safety of anagrelide in ET patients as part of the Annual Reassessment.	Annually, as part of the annual reassessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Xagrid 0.5 mg hard capsules
Anagrelide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One hard capsule contains 0.5 mg anagrelide (as anagrelide hydrochloride).

3. LIST OF EXCIPIENTS

Also contains lactose.

4. PHARMACEUTICAL FORM AND CONTENTS

100 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Shire Pharmaceutical Contracts Ltd
Basingstoke
RG24 8EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/295/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xagrid (on the outer carton only)

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xagrid® 0.5 mg hard capsules
anagrelide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Xagrid is and what it is used for

Xagrid contains the active substance, anagrelide. Xagrid is a medicine which interferes with the development of platelets. It reduces the number of platelets produced by the bone marrow, which results in a decrease in the platelet count in the blood towards a more normal level. For this reason it is used to treat patients with essential thrombocythaemia.

Essential thrombocythaemia is a condition which occurs when the bone marrow produces too many of the blood cells known as platelets. Large numbers of platelets in the blood can cause serious problems with blood circulation and clotting.

2. What you need to know before you take Xagrid

Do not take Xagrid
- If you are allergic to anagrelide or any of the other ingredients of this medicine (listed in Section 6). An allergic reaction may be recognised as a rash, itching, swollen face or lips, or shortness of breath;
- If you have moderate or severe liver problems;
- If you have moderate or severe kidney problems.

Warnings and precautions
Talk to your doctor before taking Xagrid:
- If you have or think you might have a problem with your heart;
- If you have any problems with your liver or kidneys;
- If you are pregnant or breastfeeding;
- If you have been told by a doctor that you have an intolerance to some sugars.

In combination with acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, also known as aspirin), there is an increased risk of major haemorrhages (bleeding) (see section “Other medicines and Xagrid”).

Other medicines and Xagrid
Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Tell your doctor if you are taking any of the following medicines:
- Fluvoxamine, used to treat depression;
- Omeprazole, used to treat gastro-intestinal problems like reflux oesophagitis and duodenal and gastric ulcers;
- Theophylline, used to treat severe asthma and breathing problems;
- Medicines used to treat heart disorders, for example, milrinone, enoximone, amrinone, olprinone and cilostazol;
- Acetylsalicylic acid (a substance present in many medicines used to relieve pain and lower fever, as well as to prevent blood clotting, also known as aspirin);
- Other medicines used to treat conditions affecting the platelets in your blood.

Xagrid or these medicines may not work properly if taken together.

If you are not sure, speak to your doctor or pharmacist for advice.

Xagrid with food and drink
Food and drink does not affect how Xagrid works. For information on how to take your medicine, please refer to section 3.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant or are planning to become pregnant. Xagrid should not be taken by pregnant women. Women who are at risk of becoming pregnant should make sure that they are using effective contraception when taking Xagrid. Speak to your doctor if you need advice with contraception.

Tell your doctor if you are breast-feeding or if you are planning to breast-feed your baby. Xagrid should not be taken while breast-feeding. You must stop breast-feeding if you are taking Xagrid.

Driving and using machines
Dizziness has been reported by some patients taking Xagrid. Do not drive or use machines if you feel dizzy.

Xagrid contains lactose
Lactose is an ingredient in this medicine. If you have been told that you have an intolerance to some sugars, contact your doctor before taking the capsules.

3. How to take Xagrid

Always take Xagrid exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The amount of Xagrid that people take can be different, and this depends on your condition. Your doctor will prescribe the best dose for you. There is limited information on the use of Xagrid in children and adolescents and therefore this medicine should be used with caution.

The usual starting dose of Xagrid is 1 mg (2 of these capsules) per day, taken as one capsule twice a day, for at least one week.

After this time, your doctor may either increase or decrease the number of capsules that you take to find the dose best suited to you and which treats your condition most effectively.

Your capsules should be swallowed whole with a glass of water. They may be taken with food or after a meal or on an empty stomach. It is best to take the capsules at the same time every day.

Do not take more capsules than your doctor has recommended.

Your doctor will ask you to have blood tests at regular intervals to check that your medicine is working effectively.

If you take more Xagrid than you should
If you take more Xagrid than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the pack of Xagrid.

If you forget to take Xagrid
Take your capsules as soon as you remember. Take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines, Xagrid can cause side effects, although not everybody gets them. If you are worried, speak to your doctor.

Serious side effects:
Severe chest pain, palpitations associated with dizziness or feeling faint, fainting, severe abdominal or gastro-intestinal pain, vomiting blood or passing bloody or black stools, breathing difficulties or shortness of breath, particularly if your lips or skin turn a bluish colour. These have not occurred commonly, but are serious conditions. **If you notice any of these side effects, contact your doctor immediately.**

Very common side effects (affect more than 1 user in 10):
Headache.

Common side effects (affect 1 to 10 users in 100):
Dizziness (rarely when standing up or getting out of bed), tiredness, palpitations (awareness of a forceful heartbeat which may be rapid or irregular), nausea, diarrhoea, stomach pain, indigestion and wind, vomiting, anaemia (a small reduction in red blood cell count and iron deficiency), fluid retention (including swelling of your ankles) or rash.

Uncommon side effects (affect 1 to 10 users in 1,000):
A feeling of weakness or feeling unwell, high blood pressure, chills or fever, heartburn, anorexia, constipation, bruising, localised swelling with fluid (oedema), weight loss, muscle aches, painful joints, back pain, reduced feeling or tingling in toes or fingers, sleeplessness, depression, confusion, nervousness, dry mouth, loss of memory, allergic coughing, breathlessness, nosebleed, lung infection, hair loss, skin itching or discolouration, impotence, or an increase in liver enzymes. Your doctor may do a blood test which may show an increase in your liver enzymes.

Rare side effects (affect 1 to 10 users in 10,000):
Heart attack, bleeding gums, weight gain, heart muscle disease, loss of coordination, difficulty in speaking, dry skin, migraine, visual disturbances or double vision, ringing in the ears, increased need to pass water at night, pain, 'flu-like' symptoms.

The following side effects have been reported but it is not known exactly how often they occur:
- Hepatitis (inflammation of the liver) with an increase in liver enzymes;
- Allergic alveolitis, including interstitial lung disease and pneumonitis (inflammation of the lungs);
- Tubulointerstitial nephritis (inflammation of the kidneys).

If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

5. How to store Xagrid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

If your doctor stops your medicine, do not keep any leftover capsules unless your doctor tells you to. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xagrid contains
The active substance is anagrelide. Each capsule contains 0.5 mg anagrelide (as anagrelide hydrochloride).

The other ingredients are:
Capsule contents: povidone (E1201), crospovidone, anhydrous lactose, lactose monohydrate, microcrystalline cellulose (E460) and magnesium stearate.
Capsule shell: gelatin and titanium dioxide (E171).
Printing ink: shellac, strong ammonium solution, potassium hydroxide (E525), black iron oxide (E172).

What Xagrid looks like and contents of the pack
Xagrid is supplied as opaque, white, hard capsules. They are marked with ‘S 063’.
The capsules are provided in bottles containing 100 hard capsules.

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This leaflet was last revised in

This medicine has been authorised under “Exceptional Circumstances”. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.

The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.