

SCIENTIFIC DISCUSSION

1. Introduction

Anagrelide hydrochloride monohydrate is a novel imidazoquinazoline originally developed as an inhibitor of platelet aggregation but subsequently found to have value as a platelet-lowering agent for the treatment of patients suffering from Essential thrombocythaemia (ET). ET is one of a number of chronic myeloproliferative disorders characterised by an elevated platelet count due to an autonomous clonal proliferation of bone marrow megakaryocytes. The underlying cause of this proliferation is unknown. Platelet function is generally normal and the cells are able to undergo aggregation and to participate in the haemostatic process in a more or less normal manner. The diagnosis is one of exclusion of reactive causes and other myeloproliferative disorders (MPDs) according to internationally agreed criteria of the Polycythaemia Vera Study Group (PVSG). The main criterion is a sustained platelet level of $>600 \times 10^9/L$ for more than two months.

It is estimated that the prevalence of ET in the European Union (EU) is 2-3 per 10,000 persons.

ET is a condition that may affect anyone at any stage of life from childhood although the median age of presentation is 60 years. Literature and clinical experience indicate a preponderance of female patients between the ages of 25 and 50 years.

Up to two thirds of patients with ET are asymptomatic and a significant number of patients are now being diagnosed as an incidental consequence of the analysis of full blood counts for other health reasons. Generally, the older patient is more likely to be symptomatic at presentation, although younger patients may present with major complications.

The clinically important consequences of thrombocythaemia include an increased risk of spontaneous thrombosis and infarction, including stroke, capillary occlusion, angina, cardiac infarction, superficial venous thrombophlebitis, pulmonary embolism, and sometimes internal haemorrhage. Thrombosis can occur for example in cerebral, coronary, peripheral, and digital arteries and splanchnic veins. Vasomotor symptoms such as headache, erythromelalgia and visual disturbance are not uncommon. Although haemorrhage is less common than occlusive events, gastrointestinal and post-operative haemorrhage may cause major morbidity. Thus thrombohaemorrhagic complications represent the major cause of morbidity and mortality. Thrombocythaemia tends to continue for many years, provided that its vascular complications do not cause the death of the patient. In patients with ET there is a 7-fold increase in thrombotic events compared to a control population.

After a long period some patients may develop more serious bone marrow disorders, including myelofibrosis and even leukaemia. The risk of transformation in the untreated disease into either myelofibrosis with myeloid metaplasia or acute leukaemia is very low, approximately 1.5%, but also a relationship between drug therapy and increased incidence of leukaemic transformation has been reported. As with many other medical conditions, the risks of the disease have to be weighed against the currently available therapies.

The dilemma in ET is how best to manage the asymptomatic and symptomatic patient facing a life long disorder. The scenario (asymptomatic patient with a life long condition) has much in common with other (often silent) diseases such as ischaemic heart disease and hypertension. Unlike these two conditions, the incidence of the disease is lower and treatment strategies are far less clearly defined. Clinical experience has shown the value of treatment once the platelet count has risen above approximately $650 \times 10^9/L$. The treatment goal is to decrease the platelet count in order to try to prevent thrombotic or haemorrhagic complications, with minimal drug toxicity. As ET is a chronic disease, there is a need for a well-tolerated long-term treatment. The standard treatment options for this disorder include the use of hydroxyurea and alkylating agents, both of which cause non-selective suppression of bone marrow elements.

Hydroxyurea (HU) has become the standard therapy for the treatment of Essential Thrombocythaemia in the absence of any other acceptable alternative. HU is the only agent that is currently approved in the European Union for the treatment of Essential Thrombocythaemia, in a limited number of member states.

Continuous treatment with HU has been demonstrated to reduce the platelet count to below $500 \times 10^9/L$ within 8 weeks in 80% of patients. The first clear demonstration that platelet-lowering cytoreductive therapy reduced the frequency of thrombotic events in a high-risk group came from a study that compared the use of HU with a non-treated control group. A six-fold reduction was found in the incidence of thromboembolic events for those treated with HU compared with the control group. This was confirmed in an updated progress report on the study five years later.

HU is generally well tolerated, but in 3-8% of patients with ET, the drug has had to be suspended due to poor compliance. HU is a non-selective myelosuppressive agent, and sometimes adequate platelet count control cannot be achieved without unacceptable reductions in neutrophil count and/or haemoglobin level. However, in the long-term, loss of platelet control (or a rebound of platelet counts) and adverse events can occur (including refractory leg ulcers with their accompanying significant morbidity). There is concern that long-term HU treatment may be leukaemogenic, especially in those patients previously treated with alkylating agents: this is an important consideration in the clinician's decision-making process when deciding whether or not to treat younger patients, typically <60 years, and those considered to be at a higher risk of thrombohaemorrhagic complications. Therefore, HU is generally used in older patients considered to be at higher risk because of the presence of other factors including a high platelet count (of $>1,000$ or $1,500 \times 10^9/L$) and presentation with, or the presence of, cardiovascular complications.

Two other non-platelet selective cytoreductive agents, busulphan and interferon alpha, are generally used in the EU 'off-label' for the treatment of ET.

Interferon-alpha has shown therapeutic activity in ET to control excessive thrombocytosis.

Advantages over current therapeutic options include lack of known leukaemogenic effects.

Nevertheless, it must be administered parenterally and has a high incidence of associated adverse effects.

Busulphan is an alkylating agent, which is well tolerated, but has leukaemogenic potential (as do all alkylating agents) and its use is therefore in principle limited to selected patients (over 70 years of age).

Several other agents are effective with a more or less rapid response: Pipobroman, P^{32} , Chlorambucil, Uracil mustard, Nitrosourea, Melphalan. However, alkylating agents and P^{32} should not be used initially, especially in younger patients, because of the leukaemogenic risk.

In conclusion, a well-tolerated platelet selective agent is clearly needed as therapeutic alternative, especially in young patients.

Anagrelide is approved for use in ET and other myeloproliferative disorders (MPDs) in the USA plus 11 other countries and has been available in 29 countries on a compassionate use basis, including more than 13 EU countries.

In the EU Xagrid (anagrelide) is approved for *"the reduction of elevated platelet counts in at risk essential thrombocythaemia 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 essential thrombocythaemia patient is defined by one or more of the following features:

>60 years of age or

A platelet count $>1000 \times 10^9/l$ or

A history of thrombo-haemorrhagic events."

Treatment with Xagrid capsules should be initiated by a clinician with experience in the management of essential thrombocythaemia (ET). The recommended starting dosage of anagrelide is 1mg/day, which should be administered orally in two divided doses (0.5mg/dose). 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 $600 \times 10^9/l$ and ideally at levels between $150 \times 10^9/l$ and $400 \times 10^9/l$. The dosage increment must not exceed more than 0.5mg/day in any one-week and the recommended maximum single dose should not exceed 2.5mg.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Xagrid contains 0.61 mg of anagrelide hydrochloride monohydrate equivalent to 0.5 mg of anagrelide as active ingredient. It is presented in hard gelatine capsules.

Other ingredients include povidone, crospovidone, anhydrous lactose, lactose monohydrate, microcrystalline cellulose, magnesium stearate.

The capsules are packaged in HDPE bottles with child-resistant cap, containing 100 hard capsules.

Active substance

The chemical name of anagrelide is imidazo[2,1-b]quinazolin-2(3H)-one, 6,7 -dichloro-1,5-dihydro, monohydrochloride. It does not contain any chiral centers and thus it does not exhibit any optical isomers.

Anagrelide HCl is an off-white powder, non-hygroscopic and poorly soluble in most organic solvents (except DMSO and DMF). However, the gastrointestinal tract rapidly absorbs anagrelide and peak plasma concentrations are obtained about 1 hour after the intake.

There is no evidence of polymorphism of the active substance despite carrying out the traditional polymorphism promotion studies using recrystallisation from various solvents. Upon heating, the salt is susceptible to loss of hydrogen chloride and reversion to the free base.

There are five synthetic steps in the manufacture of anagrelide hydrochloride, the last being the conversion of the free base to the hydrochloride monohydrate. Then anagrelide HCl is subject to milling.

The starting material and three intermediates of the synthesis are controlled in the active substance. There are two other potential impurities, which could be formed in the final step of the synthesis.

Active substance specification

The active substance specification includes tests for description, identity (IR), assay (HPLC), moisture (Karl Fischer), related impurities (HPLC), residual solvents (GC), heavy metals (USP) and particle size.

The analytical methods used in the routine controls have been validated and thus considered to be suitable. The impurity levels limits are justified by toxicological studies.

A summary of the finished particle size data for 17 batches has been provided. The results show that micronisation of anagrelide HCl is very reproducible.

It has been proved that the tests and limits in the specification are appropriate for controlling the quality of the active substance.

Stability

The parameters tested were water content, assay and impurities using the same methods as for release, which were stability indicating. Seven batches were stored at 25°C/60% R.H. for 60 months, at 30°C/60% R.H. for 12 months, and at 40°C/75% R.H. for 6 months. Additional conditions tested were 30°C for 60 months, 40°C and 50°C for 6 months.

Anagrelide HCl was stored in double polyethylene bags and placed within fiberboard drums. When stored under the various conditions described above, anagrelide HCl is stable and no particular trends are observed. A validated retest period has been assigned.

Other ingredients

All ingredients are tested to, and comply with, Ph Eur Requirements. Three excipients are of animal origin: magnesium stearate, lactose and gelatin. The applicant provided a CEP for magnesium stearate, gelatin and lactose. Confirmation is also provided from the supplier of lactose that the milk is sourced from healthy animals in the same conditions as milk collected for human consumption.

Anagrelide capsules are packaged in HDPE bottles containing a cotton coil filler and dessicant. Closure is a plastic child resistant cap with heat sealable foil lining.

Product development and finished product

The development studies focused on four critical points: the active substance content uniformity, the development of a formulation, which could be filled in hard gelatin capsules, dissolution and stability of the finished product.

Given the poor solubility and the low active dose of anagrelide, it was expected that finer particles were needed to faster dissolve and to more uniformly disperse in the formulation. For this reason micronisation has been performed and particle size specifications have been set. The justification of these specifications is based on retrospective data presented on 17 anagrelide batches.

Commonly used excipients have been employed in the formulation. The compatibility between the active ingredient and the different excipients has not been investigated, but the stability studies indicate the suitability of the excipients in combination with the active ingredient.

All batches used in the pivotal clinical studies have the same formulation as the product intended for the market.

The manufacturing process is a standard wet granulation process followed by milling, blending and capsule filling and was chosen in order to improve the dissolution performance and the content uniformity results. In process controls are stated. Validation data from four full-scale batches and two full scale batches manufactured in the final premises have been presented. The validation concerned the drying, mixing and filling step as well as the encapsulation operating parameters. All batches met the acceptance criteria for the release of the final product and all pre-defined quality and performance specifications established in the approved validation protocol were met.

Product specification

The products specifications include tests by validated methods for appearance, identification (HPLC), assay (HPLC) degradation products (HPLC), average mass, uniformity of content (Ph.Eur.), dissolution and microbial purity. Batch analysis data from 35 production scale batches were presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

The specification of the finished product complies with the requirements set in the current guidelines and batch analysis data confirm satisfactory uniformity.

Stability of the product

All stability studies were conducted in compliance with ICH requirements. The batches are tested for description, average capsule weight, assay, impurities and dissolution.

Three validation batches were monitored up to 6 months under accelerated conditions (40 °C/75 %RH) and up to 5 years at 25 °C / 45 % RH. The first 4 production batches have also been monitored according to the ICH guidelines with up to 36 months long-term stability. Two additional batches are being monitored for up to 5 years under long-term conditions

The stability data indicate that anagrelide capsules 0.5mg, packaged in the intended marketed pack (HDPE bottles with desiccant, cotton coil and polypropylene cap) maintained their physical integrity and potency and there were no significant changes in the dissolution results. As suggested by the results obtained from all batches, the proposed shelf life for the commercially packaged product under the conditions specified in the SPC is acceptable.

Discussion on Quality aspects

The development of Xagrid has been undertaken over a long period and the greatest part of it prior to Note for Guidance on Development Pharmaceuticals. However all critical aspects have been studied and the quality of the product is adequately established.

The active substance is stable; it is well characterised and documented. The excipients are commonly used in this kind of formulation and the packaging material is well documented. The manufacturing process of the finished product has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. However at the time

of the CPMP opinion a number of minor quality issues were unresolved. The applicant gave a commitment to resolve these issues as post opinion follow up measures.

3. Part III: Toxicopharmacological aspects

GLP

The preclinical data package included many studies that were undertaken prior to the introduction of GLP requirements. While the absorption and tissue distribution studies were not carried out according to GLP principles, all other pharmacokinetic studies and most toxicity studies were GLP compliant. The pivotal studies that support the clinical use of anagrelide (repeat dose studies of 1 and 12 months duration in rat and dog, reproductive toxicology studies and mutagenicity studies) were conducted in compliance with GLP regulations. A small number of GLP-compliant studies were conducted with a human metabolite of anagrelide, RL603.

Pharmacology

Primary pharmacodynamics

In vitro studies

Anagrelide has been shown at therapeutic plasma concentrations (5-50 ng/ml) not to affect the mitotic development of early megakaryocyte precursors but to reduce the megakaryocytes development during the later postmitotic phase. It exerted a profound effect on megakaryocytes maturation reducing both megakaryocytes ploidy and diameter. The primary pharmacological effect of anagrelide is inhibition of the maturation of megakaryocytes leading to a reduction in platelet synthesis. These results have been confirmed *in vivo*.

The factors that regulate megakaryocytes differentiation and development are still unknown. Thrombopoietin is the principal humoral agent involved in megakaryocyte development and platelet production. It is acting via its receptor c-mpl, which triggers on signal transduction the megakaryocytes proliferation and maturation. Anagrelide is a specific inhibitor of the c-mpl receptor of thrombopoietin. This inhibitor effect is dose related (5 ng/ml to 5 µg/ml). Anagrelide failed to inhibit IL-3 stimulated proliferation of megakaryocytes. This system thrombopoietin-c-mpl receptor is species specific, which could explain in why anagrelide acts only in man and not in other animal species.

The main metabolite in all species is RL603 (2-amino-5,6-dichloro-3,4-dihydroquinazoline), which initially was considered responsible for part of the inhibitor effect of anagrelide. However, later studies confirmed that RL603 does not contribute to platelet lowering activity.

In vivo studies

Most early reports suggested that anagrelide (and its metabolite, RL603), did not have any effect on blood platelet numbers in animals. However, careful examination of the toxicology data (see table below), obtained after administration of anagrelide showed evidence for some reduction in the number of blood platelets although this was not of the same magnitude as in man.

Maximum treatment-related change in platelet count during toxicity studies with anagrelide hydrochloride

Study number and description:	292-96-006 1-year dietary rat		R00074-SPD422 4-week dietary rat		292-96-005 ^a 1-year capsule dog		D00075-SPD422 week capsule dog	4-
Occasion:	Week 13		Week 4		Week 39		Week 4	
mg salt/kg/day	Dose	Count	Dose	Count	Dose	Count (%)	Dose	Count
Platelet count (10 ⁹ /L)								
Males	0	1123	0	1108	0	278 (11%)	0	302
	120.5	1024	5	1125	10	276 (41%)	1	298
	361.5	905	50	980*	300	224 (47%)	10	298
	1205	1023	120	903**	600	193 (47%)	100	280
	#	#	360	988**	#	#	300	235*
Females	0	1050	0	1113	0	292 (21%)	0	329
	120.5	873	5	1125	10	353 (38%)	1	355
	361.5	921	50	941*	300	281 (38%)	10	237
	1205	774**	120	1008*	600	249 (24%)	100	260
	#	#	360	970*	#	#	300	204*

^a The effect in the one year dog study was most apparent when counts were expressed as a percent of the pre-treatment value.

Three treated groups only

\$ Percentage change from predose

Statistical significance : * P<0.05, ** P<0.01

Secondary pharmacodynamics and safety pharmacology

At *in vitro* doses of 1 µM, higher than those used to reduce platelet numbers in man (10 nM), anagrelide inhibits platelet aggregation by inhibition of cAMP PDE III in platelets. The effect on platelet aggregation occurs to a similar extent in animal and human blood. The metabolite RL603 has no inhibitor effect on the inhibition of platelet aggregation. Anagrelide produces the same effect on platelets as other inhibitors of cAMP PDE III such as amrinone and milrinone, and agents that stimulate adenylate cyclase such as prostaglandins E₁ and I₂. Vasodilatation and positive inotropy also arise from inhibition of c-AMP PDE III. The metabolite RL603 has no inhibitor effect on inhibition of platelet aggregation. A series of studies illustrate the positive inotropic, chronotropic and vasodilatory activity of anagrelide consistent with the inhibition of phosphodiesterase in cardiac and vascular muscle.

Anagrelide did not significantly inhibit HERG tail current in HEK 293 cells transfected with HERG cDNA, suggesting no potential for prolongation of QT interval. In the doses for which, in rat and dog, cardiovascular effects are observed, the margin above the anagrelide exposure in subjects who received 1 mg anagrelide tid was about 13 fold for rat and about 3.4 fold for dogs on an AUC₀₋₂₄ basis.

Human exposure to RL603 is substantially greater than to anagrelide. At the lowest doses tested (5 mg/kg in rat and 1 mg/kg in dog), the margin above the RL603 exposure in subjects who received 1 mg anagrelide tid was about 2 times for rat and dog on an AUC₀₋₂₄ basis.

At high concentrations (1-100 µg/ml) anagrelide mixed with dog blood *in vitro* had no effect on erythrocytes or clotting time. The higher doses reduced platelet loss over 30min, and the lower dose had no effect. In contrast in guinea pigs, anagrelide 1-10mg salt/kg led to a dose-related increase in bleeding time; anagrelide at 10mg salt/kg was comparable to aspirin at 10mg/kg.

The safety pharmacology programme undertaken showed no effects of anagrelide on CNS in dogs at doses of 10 mg/kg. Further, in anaesthetised dogs, anagrelide 10 mg/kg ID did not affect airway resistance. Anagrelide showed a weak competitive inhibitor effect of 5-HT-induced contraction in the rat gastric fundus. In volume-loaded normotensive rats, 3-30 mg/kg anagrelide produced a fall of up to 71 % in urine output and up to 67 % in sodium output over 4 hours.

Pharmacodynamic drug interactions

The modest inhibitory activity of anagrelide towards CYP1A2 might indicate a potential for interaction with other co-administered drugs, which are primarily cleared by this enzyme such as theophylline and imipramine. RL603 showed considerably less inhibitory activity towards CYP1A2 than anagrelide. Anagrelide is also primarily metabolised by CYP1A2 and co-administered drugs and

dietary substances, which may be more potent inhibitors of this enzyme may reduce the clearance of anagrelide e.g. omeprazole, ciprofloxacin, fluvoxamine and grapefruit juice.

In an *in vitro* study the anti-aggregatory effects of aspirin (100 µM) were clearly evident in response to collagen but were not (synergistically) increased by the presence of anagrelide. In contrast, anagrelide in this *in vitro* system, showed only weak anti-aggregatory activity even at very high concentrations (>100 ng/ml), which were increased only additively in the presence of aspirin. RL603 was without anti-aggregatory activity consistent with a lack of PDEIII inhibitory properties.

There is a limited potential effect of anagrelide in potentiating the anticoagulant effect of heparin.

The combination of a single noneffect dose of anagrelide (0.03 mg salt/kg ID) with an experimental Ca⁺⁺ channel blocker BMY-20064 (1m g/kg ID) in dogs significantly increased the coronary blood flow and ventricular contractile force produced by BMY-20064 alone. With respect to the interaction with heparin, anagrelide (10 mg salt/kg PO in the rat) was found to significantly potentiate the anti-coagulating effects of heparin. These studies suggest a potential for anagrelide to enhance the actions of these agents although no untoward effects have been seen in the clinical usage of anagrelide.

Pharmacokinetics

Absorption

Only indirect evidence of the extent of absorption of anagrelide is presented. However, the available toxicokinetic data and the clinical pharmacokinetics provide evidence of the oral absorption. In rats treated PO at 5 mg base/kg, 37% of the administered radioactivity was recovered in the urine. In rhesus monkeys treated PO at 4 mg salt/kg or IV at 1 mg salt/kg, 54% and 73 % respectively of the administered radioactivity was recovered in the urine indicating at least 74% of the oral dose was absorbed. While no comparable iv/oral data are available in dogs, toxicokinetic studies after doses of 1 and 10mg salt/kg (in capsules) have shown mean T_{max} values of 1.5 and 4h respectively suggesting rapid and therefore possibly extensive absorption. After higher doses of 100 and 300mg salt/kg T_{max} was achieved somewhat later suggesting a slower dissolution rate limited absorption, as would be expected for such a highly lipophilic drug.

Pharmacokinetics of anagrelide and RL603 following a single oral dose

Species/dose	Mean pharmacokinetic parameters				
	Analyte	AUC _{0-inf} ± SD (ng·hr/mL)	C _{max} ± SD (ng/mL)	T _{max} ± SD (hours)	t _{1/2} ± SD (hours)
Dog ² (males) 1mg salt/kg/day	Anagrelide RL603	38 ± 13 142 ± 15	10.17 ± 2.86 25.05 ± 8.0	1.5(median) 1.5(median)	3.0 ¹ 2.9 ¹
Rabbit ³ (females) 1mg salt/kg/day	Anagrelide RL603	124 ± 66 679 ± 153	40.37 ± 34.6 188 ± 88	1(median) 1.5(median)	1.7 ¹ 2.0 ¹
Man ⁴ 1mg total dose	Anagrelide RL603	12.15 ± 6.88 57.47 ± 32.47	4.71 ± 2.6 7.31 ± 3.2	1.17 ± 0.5 2.56 ± 1.04	1.36 ± 0.35 5.60 ± 1.06

¹calculated as ln2/(mean rate constant)

²report no. D00075-SPD422-IIIA

³report no. L000076-SPD422-IIIA

⁴report no. X00358 SPD422 –IV

⁵ report no 292-063, not into the original table, added by the assessor

Distribution

Substantial plasma exposure to both drug and major metabolite (RL603) was demonstrated in rats, dogs, and rabbits. Exposure with respect to dose varied between species with rabbits displaying the highest levels. In rats, females tended to produce somewhat lower $C_{\max}$ and AUC values for both drug and metabolite (RL603) while in dogs, general exposure tended to be higher in females. Exposure to both drug and metabolite appeared to increase in a disproportionately greater manner with dose suggesting possible saturation of other clearance mechanisms in favour of conversion to RL603 although this was more evident at the higher doses used in animals.

The binding of both anagrelide and its major human metabolites to plasma proteins was measured in rats, dogs, rabbits (concentrations up to 5000 ng/ml) and man (concentrations up to 1000 ng/ml). Neither anagrelide, nor its major human metabolites RL603 and SPD604, are extensively bound to plasma proteins and as such drug-drug interactions as a result of plasma protein binding displacement are unlikely.

A quantitative tissue distribution study conducted in the rat after oral administration of ^{14}C -labelled drug at 5 mg base/kg showed higher radioactivity than in plasma from 21 h to 72 h in blood cells, kidney, liver, lungs. The lowest levels of tissue localisation were seen in the eyes, gonads and brain. No significant persistence of drug related material was evident in any tissue with concentrations generally falling to less than 10% of their 2h levels within approximately 21h of dosing.

Metabolism

Biotransformation of anagrelide appears to be very extensive in all species examined with negligible amounts of the drug being excreted unchanged. There appears to be at least five metabolites in rat and dog urine including RL603 (and its glucuronide), the keto aldehyde SPD604 and the products of hydroxylation of the quinazoline ring. In man, metabolism appears to be rather simpler than in rats or dogs with just three major components comprising the N-glucuronide of RL603, RL603 itself (the most abundant), SPD604 and a small amount of unchanged drug in urine.

RL603 does not contribute to the platelet lowering activity. *In vitro* screening against a broad range of receptors and enzymes showed little or no activity of RL603 on these systems.

Despite the rapid and extensive *in vivo* metabolism, *in vitro* studies using human hepatocytes showed evidence of only very slow bioconversion. Using various expressed human cytochrome systems only CYP1A2 appeared to metabolise the drug but very slowly. Subsequently *in vitro* studies using human liver microsomal preparations and model substrates for the major cytochromes showed that anagrelide (but not RL603) appeared to inhibit the actions of CYP1A2. This inhibition occurred in the range of concentrations previously used to study the potential *in vitro* metabolism of the drug and probably explains the initial lack of *in vitro* metabolism of anagrelide. With just a short (15 min) pre-incubation period this inhibition amounted to some 60% at 18.8 μM ($\sim 4.8\mu\text{g/ml}$).

In contrast to these human *in vitro* studies, Arochlor 124 induced rat liver S9 (used in the *in vitro* mutagenicity screens) showed extensive metabolism of anagrelide to RL603 and SPD604 providing reassurance that such S9 incubates used in the *in vitro* genotoxicity screens would have resulted in exposure to both of these human metabolites of the drug.

Excretion

Mean radioactivity recovered from 0 to 72 h in 4 male rats after 5 mg/kg PO was 37 % in urine and 50 % in feces (total = 88 %), 97 % of the total radioactivity was excreted in 48h. In one other group of 3 rats, recovery was 37 % in urine, 52 % in feces and 1.4 % in carcass (total = 90 %). In the rat there is evidence for biliary secretion from the significant amount of radioactivity appearing in the faeces after i.v. dosing (approximately 44%).

In studies in which the aim was to study metabolism, rat (n = 6), dog (n = 2) and monkey (n = 2), 75 $\mu\text{g/kg}$, dose 27 $\mu\text{g/kg}$ and 48 $\mu\text{g/kg}$ orally respectively, % dose eliminated in 24 h urine were 40 %, 25 % and 60 % (292-060). Following a 50 mg salt/kg dose to rats and dogs, urinary excretion accounted

for approximately 25% and 10% of the dose respectively. However, clearance in rat and dog cannot be estimated because of the lack of IV data. In 2 monkeys it was 0.04 – 0.02 l/h. Estimated elimination $t_{1/2}$ are 3 h in dog, 1.9 in rabbit and 51 h in monkey. However, it should be noted that the data in monkeys are unreliable since no validation of the bioanalytical method was undertaken. The PK parameters quoted here are almost certainly a reflection of contamination of the drug levels by co-eluting metabolites.

Pharmacokinetic drug interactions

In vitro studies using human liver microsomal preparations and model substrates for the major cytochromes showed that anagrelide (but not RL603) appeared to inhibit the actions of CYP1A2 on its model substrate ethoxyresorufin. These results suggest anagrelide could elicit an inhibitory effect on its own metabolism, leading to a decrease of its clearance in repeated dose and consequently to an increase of the plasma concentration.

No effects were seen in dogs on the kinetics of either anagrelide or hydroxyurea in the presence of the other when administered in the ratio of the clinically used doses (total doses of 2 mg anagrelide and 500 mg hydroxyurea).

Toxicology

Single dose toxicity

Single oral doses of anagrelide were well tolerated with no deaths except in mouse dosed at 500 mg base/kg IP. Necropsy showed evidence of hemorrhagic ulceration of the gastro-intestinal tract. Signs of toxicity in other species were minimal, sporadic vomiting and diarrhoea in dogs and soft stools and inappetance in monkeys. These data provide reassurance on the acute toxicity of anagrelide in man, given the MHRD of <10mg/day.

Repeat-dose toxicity

The majority of the changes observed in the repeat dose toxicity studies can be attributed to the inhibition of cAMP phosphodiesterase III (PDEIII). It has been demonstrated that the inhibition of PDEIII leading to an increase in CAMP in platelets occurred with an IC_{50} of $5.4 \pm 1.4 \cdot 10^{-8}$ mol/ml. This inhibition was shown to be implicated in the decreased aggregation of platelets induced by anagrelide. The IC_{50} was of a similar magnitude in a variety of animal tissues. Sporadic evidence of reduced platelet aggregation or enhanced bleeding was observed.

In the rat cardiac fibrosis and myocarditis was observed at 1000 mg/kg after 27 days. Increased incidence of cardiomyopathy was observed at 1205 mg/kg in the 12-month study in the rat. In monkey no histopathological changes were found in heart after 3 months of anagrelide administration at 12 mg/kg. At this dose the C_{max} was estimated to be about 360 ng/ml, which constitutes a safety margin of 50-100 fold as compared to the human therapeutic exposure.

In the dog, mild to marked, dose-related increases in heart rate (108-131 → 135-200 bpm) with a strong and rapid pulse were noted during the 1-month study at all dose levels (1, 10, 100 and 300 mg/kg). The severity of these events diminished as the study progressed. Evidence of a reduced blood pressure was seen only in males at week 4. Subendocardial haemorrhage, fibroblast proliferation and inflammation with focal myocardial degeneration and oedema occurred at 10 mg/kg/day and above. At 1 mg/kg/day 1/6 dogs had minimal changes. In the 12-month dog study endocarditis, cardiac valve inflammation, haemorrhage and proliferative lesions of some coronary arteries occurred at 300 mg/kg/day and above. 1/8 dogs at 1 mg/kg/day was affected.

In the 12-month rat study adrenal gland enlargement could be observed in all treated males and benign pheochromocytomas were present in 3/19 males at the HD and 2/17 males and 1/18 females at MD. Medullary hyperplasia only occurred at all dose levels in males. No effects on the adrenal medulla were observed in dogs.

Anagrelide had some effect on renal function, namely diuresis and plasma electrolyte excretion in rats and 50 mg/kg and above in the 1-month study and in the 12-month studies. Increased kidney weight indicated an increased renal load in rats at 50 mg/kg and above. Responses to water loss consistent with diuresis included increases in plasma creatinine, urea, haematocrit, haemoglobin and red blood cell count. NOEL for the changes associated with diuresis in the 1-month rat study was 5 mg/kg/day. Also in the dog, changes in diuresis parameters were observed, accompanied by an equivocal increase in kidney weight. A decrease in plasma creatinine was the only corresponding change in the clinical chemistry parameters. Minor decreases in red blood cell parameters (i.e. haematocrit, haemoglobin and red blood cell count) at 4 and 51 weeks only in dogs and 100 mg/kg/day and above may have been incidental or associated with the diuresis.

There were increases in plasma cholesterol and decreases in triglycerides and a reduced incidence of fatty liver in rats at 50 mg/kg and above. Liver enlargement occurred in both rats and dogs. Higher incidences of some age-related changes of bile duct hyperplasia, hepatocellular necrosis and congestion were observed in the 12-month study. No evidence of hepatic drug-related adverse events has emerged during clinical development, or use of anagrelide.

Toxicokinetics

Plasma exposure to both anagrelide and metabolite (RL603) was demonstrated in rats, dogs, and rabbits. Anagrelide and metabolite were monitored in clinical pharmacokinetic studies allowing calculation of the multiples of the clinical exposure observed in the pivotal toxicology studies. Comparisons were made with data from male animals for consistency with the clinical data (which is from male subjects only). The plasma AUC₀₋₂₄ values in animal toxicology studies were up to 2671 times (anagrelide) and 382 times (RL603) the AUC₀₋₂₄ value in man after 1mg t.i.d. so providing evidence of substantial exposure margins in the animal safety testing programme. There was evidence of accumulation of the drug and metabolite on multiple dosing in the rat.

Interspecies comparison

The pharmacokinetics of anagrelide after oral dosing have revealed anagrelide to have a relatively short half-life of approximately 1-3 h in all species examined (man, dogs and rabbits). Rat data are not appropriate for comparison due to the dietary means of dosing. The metabolite RL603 had a similarly short half-life in animals but this was somewhat longer (approximately 5-6h) in man. The plasma 'metabolite-to-drug' ratio varied between species and the magnitude of the dose. In dogs this averaged about 4 at low dose. In rabbits the ratio was about 6.5. In rats the ratio was nearer to or slightly less than unity while in man it ranged from 5-9.

Genotoxicity

Mutagenic potential of anagrelide and RL603 was assessed in a standard battery of *in vitro* and *in vivo* studies. These studies on the genotoxic potential of anagrelide did not identify any mutagenic or clastogenic effects.

Carcinogenicity

Long-term carcinogenicity studies on anagrelide have not been conducted. An evaluation of the chemical structure of anagrelide and its main human metabolite for carcinogenic potential identified no relevant structural alerts. Furthermore, the 12-month rat toxicity study with anagrelide did not reveal any effects indicative of carcinogenic potential at doses providing a systemic exposure (AUC₀₋₂₄) that was over 2500 times greater than in patients given a 1 mg dose tid.

Reproductive and developmental toxicity

Anagrelide showed no effect on fertility in male rats (0, 60, 120 and 240 mg salt/kg/day), but in females there was an increase in resorptions and pup mortality and an increase in the duration of

pregnancy and parturition at all dose levels. The no effect dose level for maternal toxicity and reproductive effects in female rats was less than 60 mg salt/kg/day.

There was no evidence of teratogenic potential in rats (0, 100, 300 and 900 mg salt/kg) (0, 1, 10 and 20 mg salt/kg/day) but evidence of embryotoxicity (increased resorption, decreases in live foetuses and foetal weight, delayed cranial ossification) associated with reduced maternal body weight compared to controls was noted at all dose levels in rats. In rabbits adverse effects on the foetus (increased resorptions and decreased live foetuses) were noted in a preliminary study (at 60 mg salt/kg/day and above), again associated with maternal toxicity. At the no effect dose level for reproductive effects of 20 mg salt/kg, the only maternal effects in rabbits were transient variations in body weight and food intake. Separate studies in non-pregnant rats and rabbits demonstrated high levels of both anagrelide and the metabolite, RL603, in plasma at the doses used in reproduction studies, although the rat data were derived from dietary dosing.

In a peri- and post-natal study in rats the increase in maternal deaths at all dose levels (0, 60, 120 and 240 mg salt/kg/day) was associated with erosions of the gastric mucosa or prolonged gestation and difficulties at parturition. In consequence, the number of still births and deaths in the first 4 days post partum was increased and live litter sizes were reduced at all dose levels. The increase in parturition time is consistent with phosphodiesterase inhibition by anagrelide causing smooth muscle relaxation via increases in cAMP. The inhibition of uterine muscle contraction was considered to be responsible for prolongation of parturition and decreasing offspring viability.

Ecotoxicity/environmental risk assessment

An environmental assessment concluded that due to the limited patient numbers and low dose, use of anagrelide will not represent a risk to the environment and therefore no formal ecotoxicological studies have been conducted. Based on the action limit for PEC surface water of 10 ng/l, anagrelide hydrochloride is unlikely to represent a risk for the environment following its prescribed usage in patients.

Discussion on non-clinical aspects

Anagrelide is a platelet-lowering agent showing selectivity for megakaryocytes. Its mechanism of action appears to be through primary inhibition of TPO/c-mpl receptor-mediated events in megakaryocytes leading to reduced maturation of the megakaryocytes and ultimately reduced platelet numbers.

Although the pharmacokinetic package provided is rather limited, the toxicokinetic data and clinical pharmacokinetic studies provide adequate evidence that anagrelide is extensively absorbed. Anagrelide inhibits and is metabolised by CYP1A2. However, the inhibition occurs at much higher levels than those expected at therapeutic exposure (about 900-fold) and is therefore considered not relevant for the clinical exposure. The presence of the human metabolites (RL603 and SPD604) in rat and dog plasma confirms, from a metabolic perspective, the suitability of these species as appropriate toxicological models for human safety evaluation. No drug-drug interactions were identified between anagrelide and hydroxyurea or aspirin.

A comprehensive programme of toxicology studies has been conducted with anagrelide, apart from carcinogenicity testing which was omitted. High-dose selection for the pivotal studies was based on the results of preliminary non-GLP studies conducted to establish the maximum tolerable dose. Minimal plasma level data were obtained from the 12-month studies but estimates of systemic exposure can be extrapolated from the 1-month rat and dog studies. The low doses in some studies, including the 12-month studies, were set substantially above clinical doses/exposures, and in some cases this precluded the identification of a no-adverse effect dose level. Further, studies specifically addressing allergenic or immunogenic potential have not been conducted. However there was no evidence from the toxicity or general pharmacology studies that anagrelide has any effect on immune function or allergenic action and no relationship between the use of anagrelide

and such effects has been reported in patients. As anagrelide does not absorb significantly in the UVA region (320-400 nm) its phototoxic potential is low.

The most important adverse effects identified in the pre-clinical safety evaluation programme consist of effects on the cardiovascular and the reproductive systems.

The phosphodiesterase (PDE) in platelets is similar to a myocardial enzyme that regulates contractility. Inhibition of this heart enzyme entails increased intracellular cAMP levels and Ca^{2+} levels in the myocardium. Taken together with the hypotensive properties associated with peripheral smooth muscle relaxation, this mechanism is believed to be responsible for the inotropic, chronotropic and vasodilatory actions of anagrelide and the increased heart-related toxicity observed in the dog studies. After oral administration to the conscious dog, the minimum dose affecting blood pressure was about 1mg salt/kg. At this dose, other studies have shown that peak plasma concentrations of Anagrelide and RL603 are 3- and 7-fold respectively greater than those in man after a 1 mg tid dose.

Although the dog is sensitive to drugs that affect cardiovascular function, the properties of anagrelide suggest a potential to increase cardiac workload and oxygen demand in man. The potential for inotropic and hypotensive effects of anagrelide should be considered when administering concurrently with other drugs that affect the cardiovascular system or to susceptible patients and anagrelide should be used with caution in patients that have cardiovascular disease or who otherwise have an increased susceptibility to cardioactive drugs (see clinical discussion). Moreover, the histopathological changes observed in the dog study (30-day and 52-week), not only in the myocardial area but also in the pericardium, should be noted.

While there is no evidence of prolongation of QT interval by anagrelide itself there was an indication from an *in vitro* study that RL603 produces some slow onset inhibition of the HERG tail current. However this occurred at concentrations well above those circulating in plasma and, consistent with this, no effects on QT interval were seen *in vivo* in animals or in Phase 1 clinical studies. Therefore, the risk for QT prolongation due to anagrelide administration or of RL603 administration can be considered to be minimal.

Anagrelide did not significantly affect respiration or autonomic responses in the dog. Further, a simple evaluation in the dog did not show any effects on behaviour, and that plus information from other toxicity tests can suffice to exclude important effects on the CNS. No formal examination has been made of effects on the gastrointestinal tract, but the lack of findings in the toxicity studies adequately excludes any notable effects, except at high doses.

The renal effects of anagrelide are hypothesised to be mediated through the PDE inhibition as these enzymes are intimately involved in the regulation of renal function largely through cAMP- (PDEII) or cGMP (PDEV) mediated stimulation of the secretion of atrial natriuretic peptide and aldosterone. As observed in the anagrelide studies, the main consequences of PDE inhibition on renal function are diuresis and natriuresis. Although anagrelide appears to be highly selective for PDEIII, selectivity may be substantially reduced at the high doses administered in the toxicity studies and up to now anagrelide's action on PDEV is unknown.

Smooth muscle relaxation and increased levels of cAMP can stimulate fluid secretion into the intestine, a mechanism that may be responsible for the occurrence of soft faeces. Consequently, loose stools, diarrhoea and emesis have been observed in dog and monkey, and these may indicate a potential for effects on gastrointestinal function in patients.

The observed vaginal dilatation in rats may also be the result of smooth muscle relaxation and may be linked to the delays in parturition noted in some reproduction studies.

Although the mechanism remains unclear, inhibition of PDE resulting in increased levels of cAMP and consequently increases in adrenalin may provide the proliferative stimulus for hyperplasia and pheochromocytoma, as has been reported for other PDEIII inhibitors, such as ismazoel and indolidan. The reduced incidence of pituitary adenomas in male rats at 1205 mg/kg in the one-year study is consistent with this mechanism. Pheochromocytomas and hyperplasia are induced in rats by a wide

range of non-genotoxic agents, and although the mechanism remains unclear, the unusual sensitivity of the rat medulla, the ubiquitous nature of some of the inducing agents and the lack of any human counterpart of the rat lesion suggests that this increased incidence of pheochromocytomas observed in the anagrelide-treated rats, could have little to no relevance for the human safety.

In the 1-month rat study, a dose-related increase in the incidence and severity of sub-mandibular gland acinar hypertrophy and ductal cell degranulation and parotid gland acinar hypertrophy and ductal atrophy could be observed at all dose levels. Similar events have been reported in rats following the administration of cardiotonic phosphodiesterase inhibitors, which demonstrates that these changes are most probably directly related to phosphodiesterase inhibition by anagrelide.

A number of drugs, including phenylbutazone and isoprenaline, cause an increase in salivary gland size in humans, and this has not been associated with clinically significant effects. Formal clinical investigations and post-marketing surveillance have not reported any evidence for such an effect with anagrelide.

The applicant conducted a programme of studies covering all the phases of the reproductive cycle although the programme does not comply in all respects with current international guidelines. The number of evaluated females in the fertility study (8-13/group) is lower than recommended (16-20/group) and there were no assessments of reproductive function or behaviour of the offspring in the peri- and post-natal study. There were no sperm counts or assessment of sperm viability in the fertility study, but this is partly offset by the absence of histopathological change in the testis and epididymides in the repeat dose toxicity studies. There was no effect on fertility in male rats but in females there was an increase in resorptions and pup mortality, and an increase in the duration of pregnancy and parturition at all dose levels. The increase of resorptions is dose-related. Delayed cranial ossification was observed in rat at 100 mg/kg/day, but no effect was observed in rabbit at 20 mg/kg/day.

There are no pharmacokinetic data in pregnant animals and it is not known if anagrelide or drug-derived material crosses the placenta or is excreted in milk. Maximum tolerated doses for the regulatory studies were selected following preliminary studies in rats and rabbits. Anagrelide should be used in pregnancy only when the benefit to the mother justifies the potential risk to the foetus. It is not known whether anagrelide is excreted in milk, but because of the potential for adverse effects to nursing infants it is recommended that either breast-feeding is discontinued or drug treatment is stopped.

The findings in the genotoxicity tests, and in the 1-year repeated dose rat study and the absence of any structural alert, are reassuring and do justify the absence of carcinogenicity studies at the time of the marketing authorisation application (MAA). However, in order to substantiate the absence of leukomegenic potential of anagrelide as compared to the conventional therapy, the applicant should have provided more data on the underlying mechanism of this phenomenon. The applicant has therefore committed to provide information on the carcinogenic potential of anagrelide as a post-approval commitment.

4. Part IV: Clinical aspects

Pharmacodynamics

Mechanism of action

The primary pharmacological effect of anagrelide is the inhibition of the maturation of megakaryocytes, leading to a reduction in platelet synthesis: In *vitro* studies have indicated that anagrelide at therapeutic concentrations does not affect the mitotic expansion of developing early megakaryocytes precursors, but does affect megakaryocyte development during the later post-mitotic phase. Other studies showed that anagrelide exerted effects on megakaryocyte maturation, size and DNA content. Anagrelide induced left-shifted maturation and reduced both megakaryocyte ploidy and diameter.

Various studies also support that anagrelide's actions in man are specific to the megakaryocyte lineage. This specificity may relate to an interaction between anagrelide and receptor or post-receptor events triggered by the binding of thrombopoietin (TPO) to its receptor, c-mpl. No effects of anagrelide were observed in IL-3-stimulated cells or in the absence of TPO.

Primary pharmacodynamics

Five single centre, double-blind, placebo controlled studies in healthy male volunteers (studies 1772, 1773, 1775, 1776, 1777) using a single ascending dose or multiple doses for up to 28 days were conducted.

Study reference	Short title	Subjects/ patients entered	Dose (mg)	Duration
1772	Single-dose, <i>ex vivo</i> platelet aggregation	28M, aged 18-38 years	1mg, 2mg or 5mg anagrelide or placebo	Single dose
1773	Multiple-dose, <i>ex vivo</i> platelet aggregation	8M, aged 19-35 years	1 mg bid anagrelide or placebo	7 days
1775	Multiple-dose, effect on platelet count and <i>ex vivo</i> platelet aggregation	28M, aged 18-45 years	0.5mg, 1mg bid or od anagrelide or placebo	9.5 or 30 days
1776	Multiple-dose, effect on platelet count, platelet survival time and bone marrow histology	15M, aged 21-35 years	0.5mg, 1mg anagrelide bid or placebo	28 days
1777	Multiple-dose to investigate optimum dose interval and platelet reduction	24M, aged 22-49 years	2mg anagrelide tid or qid or placebo	3 days

The thrombocytopaenic effect of anagrelide was first observed in study 1773. A 1mg twice-daily dose for 7 days in 6 healthy male volunteers resulted in an average 37% decrease in platelet count from baseline. The study was terminated as a result of this finding and platelet counts continued to decline over a 3-day period following withdrawal of drug, recovering 5 days later.

Study 1775 demonstrated that oral administration of anagrelide (0.5mg or 1mg twice daily for 9.5 days or 1mg once daily for 30 days) produced a delayed, dose-related reduction in platelet count. Platelet count returned to normal one week after cessation of treatment. Platelet survival was not affected. Based on bone marrow aspirates from subjects receiving 1mg anagrelide twice daily, at day 10, it was concluded that the effect of anagrelide was not secondary to myelosuppression or megaloblastosis.

Similar effects on platelet count were reported in study 1776 were anagrelide (0.5mg or 1mg twice daily) caused peripherally circulating platelets to decrease in number.

Study 1777 provided supportive evidence that the dosing regimen proposed for the early clinical trials (anagrelide qid) was appropriate.

The above studies supported the proposal that for anagrelide to be effective in lowering platelet counts the patients should be treated for longer than 7 days.

Secondary pharmacodynamics

Platelet aggregation:

Study 1772 demonstrated the effect of orally administered anagrelide on *ex vivo* platelet aggregation induced by ADP and collagen in platelet-rich plasma of treated subjects. Doses of 1 mg, 2mg and 5mg anagrelide inhibited low ADP-induced aggregation for up to 1, 3 and 6h, respectively.

Study 1773 demonstrated the effect of anagrelide on *ex vivo* collagen- and ADP-induced platelet aggregation when administered to eight healthy subjects orally for up to 2 weeks. Placebo and anagrelide treated subjects showed similar decreases and increases in low ADP and low collagen

concentrations. However, in the absence of a meaningful statistical analysis, the provided results were considered as inconclusive.

Study 1775 demonstrated that anagrelide inhibited *ex vivo* ADP- and collagen-induced platelet aggregation from at least 1-9 h after dosing with 1mg (either once or twice daily), but had minimal effect with the 0.5mg dose (twice daily). One low value was observed 3h after dosing in one of the 3 placebo-treated subjects. In subjects who received 1mg anagrelide once daily, administration of 650mg aspirin on day 30 resulted in an additional reduction in platelet count compared to placebo.

Cardiovascular effects:

Significant falls in both systolic and diastolic blood pressure (22/15mmHg) were seen at 5mg single dose in study 1772 in normal volunteers. In the same study supine diastolic blood pressure was lowered following a single dose of 2mg. No significant changes in blood pressure were observed after a 1mg dose.

During study 1773 changes in blood pressure and pulse rate were variable and no meaningful trends were detected. Bleeding time and ECGs were normal for all subjects and no abnormal laboratory results were noted.

Study 1775 indicated that anagrelide 0.5mg or 1mg twice daily for 9.5 days resulted in a mean decrease (of 6mmHg) in erect diastolic blood pressure but no clinically significant changes in blood pressure were noted following administration of 1mg once daily for 30 days. Results were variable and increases in systolic blood pressure were observed with 1mg twice daily.

During study AGR-I-01-J, a statistically significant decrease in diastolic BP was seen at 4h in subjects treated with 0.5mg anagrelide under fasted conditions and at the 1mg and 2mg dosage level, but not in placebo-treated subjects. However, these events were not considered clinically significant.

Pharmacokinetics

Pharmacokinetic and safety data have been submitted from seven single centre phase I studies undertaken in Japan, UK, and in the USA. The provided studies were conducted between January 1979 and September 2001 in healthy male and female volunteers aged between 18 and 45 years. Subjects received single oral doses ranging from 0.5 mg to 2 mg anagrelide.

General pharmacokinetics

Study AGR-I-01-J was a Phase I, randomised, double-blind, placebo-controlled study to examine the tolerance, safety and pharmacokinetic parameters, and to assess the effect of food on the relative bioavailability of single doses (0.5, 1.0 or 2.0 mg) of anagrelide in healthy male Japanese volunteers. 26 healthy Japanese male volunteers aged 20-35 years were randomised into 3 groups as follows: 0.5mg anagrelide, fasted and fed (8 subjects) or placebo, fed and fasted (2 subjects); 1mg anagrelide, fasted (6 subjects) or placebo, fasted (2 subjects); 2mg anagrelide, fasted (6 subjects) or placebo, fasted (2 subjects).

Following an oral dose of 0.5, 1 and 2mg anagrelide after an overnight fast, anagrelide was rapidly absorbed, reaching a mean C_{max} of 2.44, 4.86 and 10.54 ng/ml, respectively, at a median time of 1h (range 0.5-2h). Approximately proportional increases in mean $AUC_{0-\infty}$ (5.72, 12.82 and 26.74ng·h/ml) were also demonstrated. Inter-subject variability in the C_{max} and $AUC_{0-\infty}$ of plasma anagrelide was observed at all dose levels, with less variability arising at the 1 and 2mg doses compared to the 0.5mg dose (fasted and fed).

RL603 reached a mean maximum plasma concentration of 3.15, 8.55 and 29.35ng/ml at a median time of 2, 3 and 2.5h following an oral dose of 0.5, 1 and 2mg after an overnight fast, respectively. There was a disproportionately greater increase in mean $AUC_{0-\infty}$ (25.24, 73.25 and 198.53ng·h/ml) as a function of dose (at the 0.5, 1 and 2mg fasted dose levels, respectively).

Following an oral dose of 0.5mg after a standard meal, anagrelide was more slowly absorbed than when dosed in a fasted state, with mean t_{max} more than doubled (2.88h *versus* 1.25h) and mean C_{max} reduced by 44% (1.35 *versus* 2.44ng/ml), although bioavailability was only reduced by 20% ($AUC_{0-\infty}$ 5.72 *versus* 4.57ng·h/ml). Similar results were seen for RL603 with a doubling in mean t_{max} (4.00

versus 1.94h), a 40% reduction in mean C_{max} (1.88 *versus* 3.15ng/mL), and 28% decrease in bioavailability ($AUC_{0-\infty}$ 18.12 *versus* 25.24ng·h/ml). There was a statistically significantly higher C_{max} ($p = 0.0179$), statistically significantly higher $AUC_{0-\infty}$ ($p = 0.0108$) and a statistically significantly earlier t_{max} ($p = 0.0028$) for anagrelide under fasting conditions compared with a standard meal given with 0.5mg anagrelide.

The mean amount (ng) of anagrelide and percentage of total dose excreted in urine 24h post-administration of 0.5mg, 1mg and 2mg anagrelide under fasted conditions was 63.4ng (0.013%), 79.2ng (0.0078%) and 129.58ng (0.0065%), respectively.

The mean amount (μ g) of RL603 and percentage of total dose excreted in urine 24h post-administration of 0.5mg, 1mg and 2mg anagrelide under fasted conditions was 114.63 μ g (32.96%), 265.85 μ g (38.23%) and 536.8 μ g (38.59%), respectively.

Absorption

Study 13970-103 was a randomised, open-label, two-way crossover study in healthy volunteers (aged 18-35 years) to evaluate the effect of food on the oral bioavailability of anagrelide. 28 healthy volunteers received a single 0.5mg dose of anagrelide on each of two occasions: one while the subject was fasted overnight, and one immediately after the subject had consumed a standard breakfast, with the order of fasted/fed dosing randomised. Administration of the two single doses was to be separated by at least a 14-day washout period.

Major changes occurred in the pharmacokinetic parameters when patients had ingested a standard breakfast compared to after an overnight fast. These changes included a clinically significant decrease in C_{max} and a clinically significant increase in t_{max} . An increase in $t_{1/2}$ elimination was statistically significant but not considered to be clinically significant. The overall effect of these changes was to broaden the plasma concentration *versus* time curve. Comparison of the AUC_{last} and $AUC_{0-\infty}$ showed that more than 90% of anagrelide was eliminated within the 12 hours following ingestion.

Elimination

Study 1774, an open-label and single-dose study in five healthy volunteers, males, aged 18-35 years, was designed to define amounts of radioactivity in blood and plasma and excreted in urine and faeces as a function of time following a single oral dose of 1mg 14 C-anagrelide, and to determine the amounts of anagrelide in plasma and urine and the urinary metabolite profile following a single oral dose of 1mg 14 C-anagrelide. No significant amounts of radioactivity were associated with the cellular components of blood. The main route of elimination was in the urine, as metabolites and 4 urinary metabolites were detected by HPLC, the main two of which (over the period 0-48 hours) accounted for 44% and 24% of total radioactivity.

Study 13970-107A objectives were to characterise the mass-balance of 14 C-anagrelide after administration of a single oral dose of 14 C-anagrelide in five healthy subjects (4 male, 1 female). Over the duration of the study the total dose of administered 14 C was recovered in the urine (78.4%) and the faeces (20.2%). Sixty-one (61) % of radioactivity given was excreted in the 24 hours following administration (57% urine, 4% faeces) and by 72 hours over 90% had been excreted. Excretion was virtually complete (>97%) by 120 hours.

Pharmacokinetic interaction studies

Studies SPD422-IV-101 and SPD422-IV-102 were two Phase I, single centre, open label, randomised, three-way crossover studies in healthy male volunteers, designed to investigate any possible effect on the plasma pharmacokinetic profile of Warfarin or Digoxin, and anagrelide and its metabolite RL603 when anagrelide (1 mg) and Warfarin (10 mg) or Digoxin (0.5 mg) were co-administered. The safety and tolerability of these dosing regimens were also assessed.

The rate and extent of absorption of Digoxin, as determined by the primary endpoints, $AUC_{0-\infty}$ and C_{max} , were not affected by the co-administration of anagrelide. However, the secondary

pharmacokinetic endpoints $t_{1/2}$, AUC_{last} and β were marginally outside the bioequivalence criteria but this was not considered to be clinically significant. The pharmacokinetic parameters of anagrelide were unaffected by the co-administration of digoxin except for the C_{max} for anagrelide which was marginally above the range for bioequivalence. The increase in C_{max} when anagrelide was co-administered with Digoxin was small and not considered to be clinically significant.

Warfarin (R and S) and anagrelide C_{max} and $AUC_{0-\infty}$ values were also not affected when the two drugs were co-administered except the C_{max} for anagrelide, which was marginally below the bioequivalence range in the presence of Warfarin. The secondary pharmacokinetic endpoints for both enantiomers of Warfarin and anagrelide were not affected when the two drugs were co-administered except for t_{max} for anagrelide and S-Warfarin which were slightly but not clinically significantly outside the bioequivalence range when the two drugs were co-administered.

Special populations

No formal studies in special patient groups (e.g. children, in subjects with renal or hepatic impairment) were performed.

Discussion on Clinical Pharmacology

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.

Anagrelide's mechanism of action as a platelet-lowering agent clearly differs from that of other agents that are used in this context, such as hydroxyurea and interferon-alpha. These agents provide a non-selective inhibition of haematopoiesis and are used to reduce the number of erythrocytes and leukocytes as well as platelets in patients with myeloproliferative disorders. Hydroxyurea is a non-selective cytotoxic agent that affects erythroid (BFU-E) and granulocytic-macrophage progenitors (CFU-GM) as well as cells of the megakaryocyte lineage. The wide-ranging antiproliferative effects of interferon-alpha are complex and do not involve a selective mechanism of action. As well as having direct cytotoxic activity there are also effects on the immunological regulation of progenitor cell growth, on gene regulation and modulation of the actions of cytokines.

The ADME properties of anagrelide are considered as sufficiently well delineated in healthy subjects. Following oral administration of anagrelide in man, at least 70% is absorbed from the gastrointestinal tract. Anagrelide absorption is rapid and unaffected by dose. The pharmacokinetics of the parent compound appear linear over the 0.5-2.0 mg dose range, while exposure to the metabolite RL603, as well as the RL603/parent drug ratio, increased with dose. However, dose did not alter the terminal elimination half-life of RL603, suggesting increased rate of RL603 formation, or saturation of other clearance mechanisms for anagrelide. 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. 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.

When a 0.5 mg dose of anagrelide was taken following food, its bioavailability (based on AUC values) was modestly reduced by an average of 14% when compared with drug administered to the same subjects in the fasted state. The peak plasma levels were reduced by 45% and occurred approximately 3 hours after dosing. Excretion of the major urinary metabolite was decreased slightly. None of these changes induced by food were considered to be clinically significant.

The preferred route of excretion was via the urine (78.4%). 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 N-(5,6-dichloro-3,4-dihydroquinazalin-2-yl)-2-oxoacetamide 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.

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.

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 cyclic AMP phosphodiesterase III (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 theoretically potentiate the effects of other medicinal products that inhibit or modify platelet function e.g. acetylsalicylic acid. An *in vitro* study in human whole blood demonstrated that the anti-aggregatory effects of acetylsalicylic acid were additively, but not synergistically increased by the presence of anagrelide. However, during clinical development, no clear indication of any such effects have been observed with acetylsalicylic acid. The applicant will undertake a study in healthy male volunteers to assess the pharmacodynamic and pharmacokinetic effects of anagrelide and aspirin when administered in combination as part of their post-approval commitments.

A preclinical *in vivo* pharmacokinetic interaction study in the dog investigating the potential effects of anagrelide and hydroxyurea when given in combination demonstrated no adverse effects on the kinetics of either medicinal product.

The potential interactions with anagrelide are adequately covered in the SPC.

Pharmacokinetic studies have not been conducted in elderly patients or in patients with impairment of hepatic or renal function. The complete absence of PK data in the elderly is a major drawback for the use of anagrelide in this population. However, 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. The applicant will provide further pharmacokinetic data from a cohort of elderly patients post-marketing.

For patients with renal and hepatic impairment the data are too sparse to conclude a safe use in these patients groups. A warning has been added in the SPC and the applicant has committed to perform additional studies post-marketing to generate pharmacokinetic data in both patients groups to obtain supplementary information.

Essential thrombocythaemia is a rare condition in children. Therefore, there have been no formal clinical studies to establish safety and efficacy in this patient population. A limited number (12) of children (age range 5 – 17 years) with essential thrombocythaemia have been treated with anagrelide during clinical development. Anagrelide should be used in this patient group with caution until further data are available.

Clinical efficacy

Overview of Clinical Trials Programme

With reference to efficacy and safety, this application is based on the results of six studies. With the exception of study 700-015, all trials are open label, non-randomised, non-comparative trials. Two studies are designed as compassionate-use studies (studies 700-999 and 13970-301). In total, 1446 patients with Essential Thrombocythaemia from these studies were evaluable for clinical efficacy. Studies 700-013 and 700-015 are considered as supportive.

As indicated in the table below, the provided studies have not only been performed in patients with ET, but also in patients with thrombocytosis associated with other Myeloproliferative Disorders.

Study reference	Short title	Study design	Patients entered	Duration
700-012	Dose-ranging in patients with ET or PV	O, SC	Total: 44 35 ET : 11 M, 24 F	Up to 4 years
700-013	Platelet reduction in patients with CML	O, SC	Total 4: 3 M, 1 F	Up to 4 years
700-014	Platelet reduction in patients with all MPDs	O, SC	Total: 498 274 ET	Up to 4 years
700-015	Comparison of anagrelide and HU in symptomatic patients	O, R, C	Total: 6 : anagrelide : 4 3 ET : 3F	72 – 773 days
700-999	Compassionate use, platelet reduction in patients with all MPDs	O, SC	Total: 455 242 ET	Up to 4 years
13970-301	Long-term efficacy and safety in patients with thrombocythaemia	O, SC	Total: 3950 2410 ET	Up to 5 years

O open-label; SC self-controlled; R randomised; C controlled; M male; F female; ET essential thrombocythaemia; PV polycythaemia vera; CML chronic myelogenous leukaemia, MPD myeloproliferative disorder; HU hydroxyurea

GCP

Given the clinical studies predate ICH GCP and the fact that the responsibility for the studies have been transferred between different sponsors, the CPMP requested a GCP inspection of study 700-014. Objectives of study 700-014 were to determine the ability of anagrelide to reduce platelet count to $\leq 600 \times 10^9/l$ and maintain it within physiological range (130 to $400 \times 10^9/l$) in patients with thrombocythaemia secondary to a myeloproliferative disorder, and to determine the incidence of untoward side effects of anagrelide in this patient population. The study was conducted between September 1988 and February 1992.

Two sites were inspected and the data of 19 patients were reviewed. The diagnosis of ET was confirmed for all patients but major/critical findings were identified for 9/19 patients, who were not excluded from the efficacy analysis. However, it is important to note that protocols of such an old study were not as rigorous as the actual defined ones.

The conclusion of the GCP inspectors was that *“the efficacy and safety data provided in the study report of the “pivotal” phase-II study (700-014) were not reliable” (see final integrated GCP inspection report).*

The applicant has provided assurance that studies (primarily Phase I) performed after 1992 have been conducted in accordance with GCP. Further, any studies that are conducted as part of follow-up measures/specific obligations post approval will be conducted to current GCP.

Main and supportive clinical studies

Main clinical studies

Studies 700-012, 700-014 and 700-999

Study 700-012 was a multi-centre, open-label, and self-controlled study in Essential Thrombocythaemia (ET) or Polycythemia Vera (PV) patients requiring platelet reduction. Efficacy was to be assessed after treatment of 4 subjects in each indication, prior to enrolling additional subjects. The study was to be terminated if no decrease in platelet count was observed after treatment of the initial 8 subjects for 2 weeks at dosages up to 4mg every 6 hours (16 mg/day). Study 700-014 was a multi-centre, open-label, self-controlled, and open-ended study for the treatment of subjects with thrombocythaemia.

Study 700-999 was an open-label, multi-centre, non-randomised, self-controlled study for treatment of subjects with ET who had failed other therapy, with enrolment on a compassionate use basis.

Objectives were the following:

Study	Primary Objective(s)	Secondary Objective(s)
700-012	-Whether platelet count can be lowered predictably in subjects with ET. -Whether a stable dose can be achieved for extended treatment	-Long-term safety data.
700-014	-To determine the ability of anagrelide to reduce and maintain the platelet count at or near physiologic range in ET subjects.	-Effect of anagrelide on symptoms of ET. -Safety of anagrelide.
700-999	-To determine the ability of anagrelide to reduce and maintain the platelet count at or near physiologic range in ET subjects.	-Effect of anagrelide on symptoms of ET.

Studies mainly included ET patients 18 years of age or older, previously treated with a platelet-reducing agent but who had a medical indication to change therapy, or who were contraindicated for using currently available platelet-reducing therapy. Pregnancy or lactation were defined as exclusion criteria. Study 700-012 included 35 ET patients and studies 700-014 and 700-999 included 274 and 242 ET patients, respectively. Only those ET subjects who were treated with anagrelide for at least 4 weeks were evaluated for a response.

Prior therapies for thrombocythaemia for study 700-012 subjects were hydroxyurea (15 subjects), Aspirin (7 subjects), and Melphalan (2 subjects). Only one subject had not received any therapy prior to enrolment. Prior therapy was unknown for 13 subjects (37.2%).

In study 700-014, prior treatments for ET were hydroxyurea (163/274, 60%), aspirin (85/274, 31%), dipyridamole (27/274, 10%), and busulfan (18/274, 7%). Sixteen subjects also had received ³²P, seven subjects received Chlorambucil, and five subjects received Interferon. Prior therapy was unknown for 32 subjects (11.7%). In study 700-999, most of patients received hydroxyurea (79.3%). Two subjects received prior therapy that was not identified.

The planned starting dosage ranged from 2 mg/day to 4 mg/day. Subsequent doses were planned to be individually adjusted to maintain platelet count <600 x 10⁹/l and ideally between 130 - 400 x 10⁹/l. Mean anagrelide dose administered at initiation of therapy ranged from 2.3 mg/day to 4.3 mg/day. Individual subject dosages ranged from 0.5mg/day to 13mg/day.

RESULTS

- Primary efficacy variables

Primary efficacy endpoints were “Complete” and “Partial response”, and “the days to complete or partial response”. “Complete response (CR)” was defined as a reduction in platelet count to ≤600 x 10⁹/L or by ≥50% from baseline value and maintenance of that reduction for at least 4 weeks. “Partial response (PR)” was defined as a 20% to <50% reduction in platelet count maintained for at least 4 weeks. Failure to respond: a less than 20% reduction in platelet count from baseline value.

Response to anagrelide treatment:

Study	N	Responders		Number of days to response	
		CR	PR	CR	PR
700-012	34	28/34 (82%)	2/34 (6%)	18.5	15.6
700-014	254	201/254 (79%)	20/254 (8%)	18.6	13.2
700-999	242	145/242 (59.9%)	24/242 (9.9%)	23.0	19.0

Oral administration of anagrelide resulted in a significant reduction in and maintenance of platelet counts from a baseline mean of 1 297 x 10⁹/L to within or near physiological range (150-400 x 10⁹/l) in the majority of ET subjects during the study.

- Secondary efficacy variables

Secondary efficacy endpoints were mainly “decrease in mean platelet count”, “platelet count rebound during treatment interruption”, “symptoms secondary to Thrombocythaemia” and “association between mean platelet count and symptoms”.

Decrease in mean platelet count:

Study 700-012: The mean platelet count for the ET ITT population just prior to initiation of anagrelide therapy was $1,297 \times 10^9/l$. These mean counts showed a progressive decrease from baseline over time on therapy.

Study 700-014: The mean platelet count for the ET ITT population just prior to initiation of anagrelide therapy was $1,045 \times 10^9/l$. Mean values up to four years showed a progressive decrease from baseline over time on therapy.

Study 700-999: By the fourth week of treatment, the mean platelet count decreased from a base line value of $1,123 \times 10^9/l$ to $684 \times 10^9/l$. For the remainder of the study, the mean platelet count ranged between 441 and $628 \times 10^9/l$.

Platelet count rebound during treatment interruption:

Treatment interruption was defined as any discontinuation in anagrelide therapy that was of 3 or more day's duration. Any interruption of less than 3 days was considered as on treatment. Rebound was defined as any increase in platelet count that occurred during treatment interruption.

Study 700-012: Of the 10 subjects, nine did not have platelet counts on the day they stopped anagrelide treatment and/or the day they restarted anagrelide treatment.

Study 700-014: Of the 70 subjects, only 14 had platelet counts on the day they stopped anagrelide treatment and the day they restarted anagrelide therapy. All subjects who had a treatment interruption experienced an increase in platelet count during the interruption period.

Study 700-999: Of the 46 subjects, only 8 had platelet counts on the day they stopped anagrelide treatment and the day they restarted anagrelide therapy. An analysis of these 8 subjects showed that while off treatment (5-79 days), there was a clinically and statistically significant ($p < 0.005$) increase in platelet count, indicating that continued treatment with anagrelide was necessary to maintain reduced platelet count.

Symptoms secondary to thrombocythaemia:

The number of reports of symptoms secondary to thrombocythaemia tended to decrease during the duration of the studies, corresponding to the decrease in mean platelet count over time on treatment. The number of subjects reporting symptoms decreased over time on treatment as well. The symptoms specifically associated with thrombocythemia are presented in the following table.

Gastrointestinal bleeding	Recurrent pulmonary embolism
Easy cutaneous/subcutaneous bruising/bleeding	Intestinal ischemia
Epistaxis	Transient ischemic attacks
Hemoptysis	Erythromegalia
Bleeding at other sites	Digital ischemia
Recurrent arterial thrombosis	Distal ischemic ulcers
Angina	Recurrent venous thrombosis
	Acral paresthesia

Thrombocythaemia related symptoms decreased dramatically after the first month of treatment. The rate of events was the same during the first month and the 11 following months. Moreover, the annual rate decreased by two fold from year 1 to year 2.

Study 13970-301

Study 13970-301 was an open-label, multicentre study, designed to determine the efficacy and long-term safety of anagrelide for the reduction and control of platelet count, and thrombohaemorrhagic symptoms, in patients with ET, PV, chronic myelogenous leukaemia (CML), or other Myeloproliferative Disorders (MPD) who entered from studies 700-012, 700-014 and 700-999 and in those not previously exposed to anagrelide who entered study 13970-301.

The planned starting dosage was 2 mg/day. Subsequent doses were planned to be adjusted to maintain platelet count between $150 - 600 \times 10^9/l$. The mean anagrelide dose administered at initiation of therapy was 2 mg. Mean daily doses of just below 2mg/day were reached by the end of month 1 and then mean doses remained fairly constant throughout the rest of the study, although there was a slight increase in the mean values up to the end of month 6. Individual subject dosages ranged from 0.5mg/day to 13mg/day.

Study 13970-301 mainly included ET patients 18 years of age or older previously treated with a platelet-reducing agent but who had a medical indication to change therapy, or who were contraindicated for using currently available platelet-reducing therapy. Pregnancy or lactation were exclusion criteria. Prior therapies for thrombocythaemia for ET subjects were mainly hydroxyurea, aspirin, busulfan, and interferon. The efficacy evaluable ET population comprised 934 patients.

RESULTS

- Primary efficacy variables

The primary efficacy endpoint for this study was only “Complete response (CR)”, which was defined as a reduction in platelet count to $\leq 600 \times 10^9/l$ or $\geq 50\%$ from baseline at least 4 weeks after dosing with anagrelide had started.

Overall, 628 of the 934 efficacy evaluable ET patients (67.2%) showed a complete response to treatment.

Complete response rates were generally consistent across the ET population subgroups, with the complete response rate ranging from 61.0 % to 70.8%. There were no significant differences in complete response rates according to age, gender or ethnicity.

- Secondary efficacy variables

Secondary endpoints were “partial response to treatment” and “time to complete or partial response”, “actual platelet count reduction”, “relationship between platelet count levels and thrombo-haemorrhagic symptoms”, “anagrelide dosing”, “use of other cytoreductive treatments”, “response to anagrelide in patients experiencing thrombotic or haemorrhagic symptoms at baseline” and “concomitant use of aspirin”.

Percentage of patients who partially responded to treatment:

Partial response rates were then defined as a reduction in platelet count of 20% to $<50\%$ from baseline and maintenance of the reduction for at least 4 weeks during the platelet reduction phase of the study. In the global analysis of sub-groups, PR rates ranged from 9.6% to 14.7%. Elevated platelet count group and treatment intolerant group had the highest proportion of patients (14.7% and 14.1% respectively) partially responding to treatment. There was globally no difference in partial response rates regarding age, gender, and ethnic origin.

Proportion of patients who completely or partially responded to treatment:

In the global analysis, 78.7% of ET patients showed either a CR or PR to treatment. All patient subgroups showed similarly high total response rates, ranging from 75.2% to 85.3%. ET patients 18 to <60 years responded slightly more than those aged over 60 years (82.1% vs 76.8%). There was globally no difference in total response rates regarding gender and ethnic origin.

Time to complete or partial response:

The median time to measured complete or partial response for ET patients was 71 days in the overall efficacy evaluable population.

Platelet count:

Mean platelet counts for ET patients at baseline were $1089.5 \times 10^9/l$. Platelet counts ranged from just above $650 \times 10^9/l$ up to $3620 \times 10^9/l$. Mean platelet counts decreased to $<600 \times 10^9/l$ by the end of month 2 and continued to decrease until the end of first year, after which counts tended to remain stable until the end of year 3. There was a further decrease in mean values after this time.

Relationship between platelet count levels and symptoms secondary to ET:

A reduction in symptoms secondary to thrombocythaemia was seen in parallel with a reduction in mean platelet counts produced by anagrelide. In the overall efficacy evaluable ET population the incidence of the thrombohaemorrhagic symptoms (epistaxis, transient ischaemic attack, GI haemorrhage, peripheral ischaemia, haemorrhage, venous thrombosis, pain, bleeding tendency, skin ulcer) were in some cases 2 – 3-fold lower during treatment than pre-treatment. The incidence of symptoms in this population during treatment were much lower than that reported in the safety population during treatment.

Anagrelide dosing:

Overall, there were no marked differences in mean anagrelide daily doses between the safety- and the overall efficacy evaluable ET population, other than marginally lower doses in the CML group (mean doses of between 1.7 – 1.9mg/day for most of the study). Mean anagrelide daily dose (range: 2.0mg/day – 2.4mg/day) in the ET subgroups did not differ significantly. No consistent dosage adjustment was required for renally impaired patients.

Supportive studies

In order to provide support for this revised indication, a subgroup analysis of ET patients from study 13,970-301 who were intolerant to their previous therapy or whose platelet count could not be controlled by their previous therapy was produced. This consisted of reproducing all the tables originally submitted with the 13,970-301 report for the patient group specified above.

RESULTS

- Primary efficacy variables

Overall, 480 of the 725 efficacy evaluable ET patients (66.2%) showed a complete response to treatment. (Platelet reduction $<600 \times 10^9/L$ or 50% reduction from baseline)
Complete response rates were generally consistent across the ET population subgroups, with the complete response rate ranging from 61.3 % to 69.1%.

There were no major differences in CR rates according to age, gender or ethnic origin.

- Secondary efficacy variables

Secondary endpoints were “partial response to treatment” and “time to complete or partial response”, “actual platelet count reduction”, “relationship between platelet count levels and thrombohaemorrhagic symptoms”, “anagrelide dosing”, “use of other cytoreductive treatments”, “response to anagrelide in patients experiencing thrombotic or haemorrhagic symptoms at baseline” and “concomitant use of aspirin”.

Percentage of patients who partially responded to treatment:

In the global analysis of sub-groups, PR rates ranged from 9.7% to 14.3%. There was globally no difference in partial response rates regarding age, gender, and ethnic origin.

Proportion of patients who completely or partially responded to treatment:

77.4% of ET patients showed either a CR or PR to treatment. All patient subgroups showed similarly high total response rates, ranging from 75.6% to 83.5%. There was globally no difference in total response rates regarding age group, gender and ethnic origin.

Time to complete or partial response:

The median time to measured complete or partial response for ET patients was 73 days in the overall efficacy evaluable population.

Platelet count:

Mean platelet counts for ET patients at baseline were $1059.9 \times 10^9/L$. Platelet counts ranged from just above $650 \times 10^9/L$ up to $3620 \times 10^9/L$. Mean platelet counts decreased to $<600 \times 10^9/L$ by the end of month 2 and continued to decrease until the end of first year, after which counts tended to remain stable until the end of year 5.

Relationship between platelet count levels and symptoms secondary to ET:

A reduction in symptoms secondary to thrombocythaemia was seen in parallel with a reduction in mean platelet counts produced by anagrelide. In the overall efficacy evaluable ET population the incidence of the thrombohaemorrhagic symptoms (epistaxis, transient ischaemic attack, GI haemorrhage, peripheral ischaemia, haemorrhage, venous thrombosis, pain, bleeding tendency, skin ulcer) were in some cases 2 – 3-fold lower during treatment than pre-treatment. The incidence of symptoms in this population during treatment were much lower than that reported in the safety population during treatment.

Anagrelide dosing:

Overall, there were no marked differences in mean anagrelide daily doses between the safety- and the overall efficacy evaluable ET population. Mean anagrelide daily dose, approximately 2mg/day in the ET subgroups did not differ significantly. No consistent dosage adjustment was required for renally impaired patients.

Study 700 015 and study 700 013

Study 700 015 was defined as an open-label, active-controlled, and randomised study. Patients entering the study were randomised to receive either anagrelide or hydroxyurea without blinding. One hundred and forty patients were planned. However, patients and physicians did not consent to treatment with hydroxyurea because of concerns about its leukaemogenic potential. Therefore, the study was abandoned after six patients had been enrolled. Platelet count was reduced by approximately 70% after 4 months of anagrelide therapy and was maintained within the specified limits for up to 26 months. Due to the small number of included patients, no conclusion can be drawn from this study.

Study 700 013 was defined as an open-label, 2-centre, non-randomised, and self-controlled phase I/II study, and was designed to determine whether anagrelide can reduce the platelet count in patients with chronic myelogenous leukaemia (CML). The inclusion of 14-25 patients was initially planned. However, only four patients were analysed (ITT), and 3 patients were evaluable. The low recruitment was due to the small number of study centres.

During the first month of therapy mean platelet count dropped by 41% from pre-treatment level.
During two months of therapy mean platelet count dropped by 69% from pre-treatment level.

Efficacy information from Authorisation for Temporary Use (ATU)

A cohort Temporary use Authorisation for anagrelide was granted in France in January 2002 and ET patients were enrolled from June 2002. The ATU indication could be considered as very close to the currently proposed indication (resistant, refractory or intolerant to hydroxyurea). Four hundred and fifty one (451) ET patients were enrolled as of March 2003. Of these 451 patients, 162 (36%) had not previously received anagrelide. Of these 162 ET patients, 75 (46%) had a baseline platelet count recorded and 30 (19%) had a post-baseline platelet count recorded.

The applicant has provided a list of tables presenting platelet count information for four groups of ET patients: all platelet count data recorded; patients with both a baseline and a post-baseline platelet count; patients with a baseline platelet count $>650 \times 10^9/L$; patients with both a baseline platelet count $>650 \times 10^9/L$ and a post-baseline platelet count.

In patients with both a baseline and a post-baseline platelet count, the mean platelet count recorded during the 91 days prior to enrolling in the study, is reduced from $889 \times 10^9/l$ to $625 \times 10^9/l$ for the 91 days following enrolment (N=28). A further reduction in mean platelet count to $566 \times 10^9/L$ is seen for the period 92 to 182 days after enrolment (N=7). Similar results are globally presented in all the provided tables.

No formal conclusions could be reasonably drawn from the ATU data as limited data on baseline platelet count are available: Of the 162 new ET patients, 75 (46%) have a baseline platelet count recorded and 30 (19%) have a post-baseline platelet count recorded but as the collection time points were not part of the CRF, they were therefore not defined. Further, it should be pointed out that the primary aim of the ATU is focused on safety aspects. Nevertheless, the provided data globally confirm a trend in favour of a platelet count decrease after anagrelide treatment in patients resistant, refractory or intolerant to hydroxyurea.

Efficacy information from publications

The applicant presented information from recent publications in support of the efficacy assessment of anagrelide. The review of the publications indicates that anagrelide reduces elevated platelet count to below $600 \times 10^9/l$. The time to response was up to a maximum of 17 weeks, similar to the response times observed in the clinical trials. Of note, the mean number of weeks to onset of either complete or partial response was approximately 2-3 weeks in studies 700-012, 700-014, and 700-999. In study 13970-301 the number of weeks to total response was approximately 10 weeks.

Discussion on clinical efficacy

The goal of treatment in patients with ET is to reduce the platelet count and subsequently to prevent and reduce the incidence of thrombo-haemorrhagic complications. Xagrid is effective in reducing the platelet count of ET patients (overall response rates ranged from 75 % to 85 % within 2 to 9 weeks according to various studied populations) and is considered by experts within the field of haematology to compare favourably to other available cytoreductive agents, which are not platelet-selective agents, which are not always well tolerated, and are associated with increased risk of long-term side effects, which can induce treatment failures.

The safety and efficacy of anagrelide as a platelet-lowering agent has been evaluated in four open-label, non-controlled clinical trials (study numbers 700-012, 700-014, 700-999 and 13970-301) including approximately 4500 patients with myeloproliferative disorders (MPDs). However, none of them is comparative. In study 13970-301 the evaluable efficacy ET population totalled 934 patients and treatment lasted for up to 5 years. Therefore, this study provided the majority of the data and is the only study performed in patients whose therapeutic status could be considered as being in line with the indication.

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. Efficacy of anagrelide was demonstrated in reducing platelet count in the majority of patients. In studies 700-012, 700-014, 700-999 and study 13970-301 the time to complete response ranged from 4 to 12 weeks. In all studies, in terms of platelet count, complete response rate was 60% -70%, and partial response ~10%.

In study 13970-301, 628 of the efficacy evaluable ET patients (67.2%) showed a complete response to treatment. Patients who became intolerant to their previous therapy, and cytoreductive drug naive patients showed a lower complete response rate compared with the other subgroups. Further, mean platelet counts decreased progressively over time from baseline levels ($1089.5 \times 10^9/l$) to $< 600 \times 10^9/L$ after receiving treatment for 2 and 3 months, respectively, during the dose titration phase of the study. Mean platelet counts decreased further but stabilised at levels between 400 and $600 \times 10^9/l$ over the duration of the study.

Two subgroups of patients within study 13970-301 were considered as being of particular interest: those patients who were intolerant to their existing therapy and those who had failed to be adequately controlled on their existing therapy. These subgroups included a significant number of patients (725) for the efficacy evaluation of the ET population. In these subgroups combined 66.2% achieved complete response (CR). The provided efficacy data indicate that there is no significant difference in the median time to complete or partial response, and in the number of complete/partial responders across the age ranges.

The number of reports of ET symptoms related to thrombocythaemia (thrombotic, haemorrhagic or vasomotor symptoms) decreased during the treatment, corresponding to the decrease in mean platelet count over time on treatment, particularly after the first month of treatment. The rate of events was the same during the first month and the 11 following months. Moreover, the annual rate decreased by two fold from year 1 to year 2. These data are reassuring in such a chronic disease even if only few patients were evaluable after two years of treatment. However, clinical benefit in terms of thrombohaemorrhagic events has not been convincingly demonstrated.

Concern was raised over the validity of the endpoints used in the studies. The reduction of platelet count to $\leq 600 \times 10^9/l$ or by $\geq 50\%$ from baseline value has not the same therapeutic meaning, since a significant number of patients have generally platelet count over $1.5 \times 10^9/l$. Literature data suggest that complete response definition could have been platelet decrease under $400 \times 10^9/l$ (within the upper limit of the physiological range) or at least under $600 \times 10^9/l$, without taking into consideration a reduction by $\geq 50\%$ from baseline value. However, it should be acknowledged that definitions of response rates was, and is still not, standardised and various definitions of a complete and partial response can be found in the literature. Furthermore, medical practice at the time of the conduct of the studies aimed to bring about a significant reduction in platelets, generally to $\leq 600 \times 10^9/l$. It was acknowledged that the ideal objective was to reduce platelets to $\leq 400 \times 10^9/l$ or within the upper limit of the physiological range, however this could rarely be achieved.

Interruption of anagrelide treatment for more than 3 days results in a significant increase in platelet count, indicating that continued treatment with anagrelide is probably necessary to maintain a reduced platelet count. It appears that re-treatment with anagrelide can induce a re-decrease in platelet count, but no relevant information on the level of this re-increase (probably due to insufficient number of remaining patients) was available. Due to the lack of provided individual data, reasons for treatment interruption are not clear. It is also impossible to state whether or not in some cases an increase in platelet count during treatment, could be interpreted as a treatment resistance.

In some cases it was difficult to determine whether anagrelide alone was responsible for platelet decrease as there is evidence that some patients received anagrelide concomitantly with other cytoreductives. Prior to entry into study 13970-301, 31.6 % (24.8 % in the ET group and 42.4% in the non-ET group) of patients were receiving cytoreductive treatment for ET and in the majority of the cases this was hydroxyurea. It is argued that some investigators might have considered it unethical to stop treatment with hydroxyurea before commencing anagrelide treatment, as there can be a rebound effect on platelets when hydroxyurea treatment is stopped and as it may take some weeks before anagrelide is titrated to an effective dose, which will reduce platelets to the desired level. Furthermore, in order to minimise potential (or observed) side effects of hydroxyurea and anagrelide, investigators administered both drugs concomitantly in some patients as this enabled lower doses of each drug to be used whilst still adequately controlling platelet counts. 88% (200) of ET patients in the efficacy evaluable population who received hydroxyurea concomitantly only received one episode of treatment and 51% of these patients took hydroxyurea concomitantly for less than a month and a further 24% for more than a month but less than 6 months. Due to the low quality of such old protocols and studies, it would be extremely difficult to determine whether anagrelide alone was responsible for the platelet decrease in the population of patients who received hydroxyurea concomitantly.

Given the clinical studies predate GCP and the fact that the responsibility for the studies has been transferred between different sponsors, the CPMP requested a GCP inspection of study 700-014. Two sites were inspected and the data of 19 patients were reviewed. The diagnosis of ET was confirmed for

all patients but major/critical findings were identified for 9/19 patients, who were not excluded from the efficacy analysis. However, it is important to note that protocol of such an old study was not as rigorous as current ones would be expected to be. The conclusion of the GCP inspectors was that “*the efficacy and safety data provided in the study report of the “pivotal” phase-II study (700-014) were not reliable*”. Although a new efficacy and safety analysis could theoretically be performed (excluding all patients who did not meet the pre-defined inclusion criteria and all patients for whom major protocol deviations were identified), it was considered that complementary data from named patient/ compassionate use in EU would provide more pertinent information than data taken from a reanalysis of old and low quality studies. There is a wide clinical experience since anagrelide is marketed in USA since 1997, and available in EU for compassionate use. Studies performed by the applicant after 1992 were conducted in accordance with ICH GCP. Further, any studies that are conducted as part of follow-up measures/specific obligations post approval will be conducted to current GCP.

The activity of anagrelide has been sufficiently demonstrated in terms of its ability to decrease platelet counts in ET patients. The data provided from both publications/abstracts and Named patient/Compassionate Use Programmes confirm the efficacy of anagrelide: mean platelet count for new patients was reduced after enrolment in the ATU and mean platelet count for patients already controlled prior to enrolment into the ATU maintained this control on anagrelide. However, it should be pointed out that the primary aim of the ATU is focused on safety.

No comparative trial was performed with Xagrid and this omission could be considered as adequately justified by the applicant, mainly due to ethical reasons and accumulated experience. However, in order to provide further complementary data on long-term safety and efficacy the applicant will conduct a randomised clinical trial comparing the efficacy and safety of anagrelide and hydroxyurea as a post-marketing commitment.

Clinical safety

Introduction

The assessment of safety is mainly based upon clinical data from studies 700-012, 700-013, 700-014, 700-015, 700-999 and 13970-301. The purpose of study 13970-301, which provides the majority of the safety information available, was to gather efficacy and safety data on the use of anagrelide in thrombocythaemia secondary to a myeloproliferative disorder (MPD) and to provide long-term safety data in patients who entered from studies 700-012, 700-014 and 700-999 and in those not previously exposed to anagrelide.

In addition to these studies, the applicant provided data from Compassionate Use Programmes and post-marketing experience.

A cohort Temporary Use Authorisation (ATU) for Xagrid was granted in France in January 2002 and following submission of the MAA in March 2002, 451 patients were enrolled into the ATU from June 2002. Most of them correspond to the new indication, which is the scope of this MAA (this Compassionate Use Programme only included ET patients at risk who are resistant, refractory, or intolerant to hydroxyurea). The cohort ATU allows Xagrid to be made available prior to a Marketing Authorisation approval as the following conditions are met: Xagrid is intended to treat a serious and rare condition; there is a strong presumption of efficacy, an acceptable safety profile and a MAA has been filed. However, the cohort ATU provides only supportive information on the effectiveness of Xagrid and focuses on the safety. Essential Thrombocythaemia patients who correspond to the above defined indication are included in a “cohort ATU”, and are treated and monitored according to criteria fully defined in a protocol for therapeutic use and data collection.

The applicant has also provided a preliminary analysis of the safety data from the stopped anagrelide-arm of the ongoing UK MRC PT1 study (see below).

Patient exposure

4600 patients have been exposed to anagrelide during clinical trials, approximately 40 % males and 60 % females. The defined evaluable safety population comprised 3027 patients. Although the protocols stated that the patients had to be at least 18 years of age, 16 younger patients received anagrelide. The average age ranged from 57.2 to 63.6 years (range 5 to 98 years). Most of patients were aged 60 years or more (57.3% in the study 13970-301).

Adverse events and serious adverse events

26.3% of all patients experienced a serious adverse event (SAE). The ET group reported a higher percentage for drug-related SAEs (8.3%) than all patients (7.5%).

Number of serious adverse events in study 13 970-301:

	ET N= 2251	All N= 3660
Number of patients with a SAE (%)	466 (20.7)	961 (26.3)
SAEs related to study drug (%)	80 / 959 (8.3)	150 / 1997 (7.5)

SAEs occurred most frequently in the cardiac body system (6.3%) with congestive cardiac failure, in the gastrointestinal body system (3.6%) with gastrointestinal haemorrhage. The incidence of chronic myeloid leukaemia (CML) is higher in the non-ET group, but this population includes patients with CML. The inotropic and vasodilatory effects of anagrelide are considered responsible for the majority of the SAEs.

Serious adverse events with an incidence of $\geq 2,0\%$ from study 13 970-301:

	Number of patients (%)	
	ET	All
Safety population	N = 2251	N = 3660
Number of patients with a SAE	466 (20,7%)	961 (26,3%)
Cardiac	128 (5,7%)	232 (6,3%)
Cardiac failure congestive	46 (2,0%)	79 (2,2%)
Gastrointestinal	65 (2,9%)	130 (3,6%)
Gastrointestinal haemorrhage NOS	36 (1,6%)	75 (2,0%)
Blood and lymphatic system	52 (2,3%)	160 (4,4%)
Chronic myeloid leukaemia	5 (0,2%)	53 (1,4%)
Infections and infestations	59 (2,6%)	143 (3,9%)
Pneumonia NOS	36 (1,6%)	84 (2,3%)
General and administration site conditions	67 (3,0%)	149 (4,1%)
Death NOS	19 (0,8%)	52 (1,4%)
Nervous system	73 (3,2%)	125 (3,4%)
Cerebrovascular accident	38 (1,7%)	69 (1,9%)
Vascular	92 (4,1%)	189 (5,2%)
Respiratory, thoracic and mediastinal	45 (2,0%)	111 (3,0%)
Surgical and medical procedures	52 (2,3%)	98 (2,7%)
Neoplasm, benign and malignant	41 (1,8%)	82 (2,2%)

The incidence of SAEs were twice as high in the older patient population (<60 years) compared with patients aged 18-60 years. In the older patients, the most commonly recorded SAEs were cardiac disorders (congestive cardiac failure). There were no clinically relevant differences between males and females in the reporting of SAEs.

The number of patients experiencing an adverse event (AE) was nearly 100% and an average of 4.7 to 5.4 events are reported per patient. The severity of AEs as mild (38.6%) or moderate (23.9%). For all patients groups, 18.4% of all events reported were regarded as related to anagrelide therapy.

Number of adverse events in study 13 970-301

	ET N= 2251	All N= 3660
Number of patients with an AE (%)	2 242 (99.6)	3 645 (99.6)
AEs related to study drug (%)	2 184 / 10 820 (20.2)	3 330 / 18 139 (18.4)

The most common adverse event assessed as related to anagrelide by investigators was headache (13.3% to 38.3% according to the considered study). Other common drug-related AEs overall included palpitations, oedema/fluid retention, nausea/vomiting, diarrhoea, dizziness and abdominal pain. The adverse events were reported consistently across the various groups with the exception of headache which appeared at a much higher incidence in the ET population of study (14.5%) than CML group (7.7%).

The incidence of transformations to acute leukaemia / myelodysplasia syndrome in ET patients was 2.1% (47/2251). It was higher in the all patient group, mainly due to the incidence in the CML population. Most of ET patients had received hydroxyurea and/or another cytotoxic agent prior to or during treatment with anagrelide. Only 2 ET patients had received anagrelide alone but they did not have a clear diagnosis of ET at entry to the study and were already in an accelerated phase of leukaemia. There was only one ET patient who had acute myeloid leukaemia, considered as drug-related by the investigator. In nine other ET patients who also developed acute myeloid leukaemia, this was recorded as not related to study drug.

Patient with transformations of the underlying malignancy from study 13970-301

	Number of patients (%)	
	ET N = 2251	All N = 3660
Number of patients who had a transformation	69 (3,1%)	259 (7,1%)
Type of transformation		
Chronic Myelogenous Leukaemia	1 (<0,1%)	2 (0,1%)
Acute leukaemia / Myelodysplasia	47 (2,1%)	232 (6,3%)
Myelofibrosis	15 (0,7%)	19 (0,5%)
Polycythaemia	2 (0,1%)	2 (0,1%)
Unknown (lost to follow-up)	4 (0,2%)	4 (0,1%)

Discontinuation due to adverse events

In study 700-13, 100% of patients discontinued anagrelide due to either an adverse event or ineffectiveness in platelet reduction. In study 700-15, one patient discontinued because he died from myocardial infarction (death unrelated to anagrelide).

23.1% of patients withdrew due to an adverse event in the study 13970-301. There were more discontinuations from the ET population (29.2%) than non-ET (16.9%), but information about adverse events leading to withdrawal are not available in this study.

64.6% of patients were still on study after 6 months of treatment and only 1.1% after 5 years. This is explained by a high number of patients who discontinued (580 patients (31,1%) in the ET population and 1158 (38,3%) in the all population after 5 years) or were lost to follow-up (1287 (68,9%) in the ET population and 1869 (61,7%) in the all population).

Numbers of patients present (%)			
Time	ET	Non-ET	All
Baseline	1867 (100,0)	1160 (100,0)	3027 (100,0)
Month 6	1252 (67,1)	702 (60,5)	1954 (64,6)
1 Year	937 (50,2)	479 (41,3)	1416 (46,8)
3 Years	295 (15,8)	86 (7,4)	381 (12,6)
5 Years	21 (1,1)	13 (1,1)	34 (1,1)

Deaths

A total of 530 deaths were reported in the safety studies, but in most cases, they were related to the disease. Taking the ET population as a whole, a total of 25 treatment-related deaths occurred out of a total population of 2654, yielding an incidence of 0.9%. The cause of death was provided in 18 out of the 25 treatment related cases. The overwhelming majority of deaths were due to cardiovascular disease (8/18) with the remainder dying from a variety of causes including pulmonary disease, CVA, lymphoma and multi-organ failure. 8 deaths were labelled NOS (7 out of the 25 treatment related

cases and 1 unrelated): the cause of death was “unknown”, but the medical histories of these patients were provided. One patient was lost to follow-up, 6 were known to have significant co-morbidity that may have been the cause of death. One remaining patient had platelet counts over 1 million with anaemia and leucopenia. There are no unexpected findings in the ET population as a whole (related and unrelated deaths). The 6 most frequent Body Systems reported for cause of death can be ranked from highest to lowest: cardiac, cerebrovascular, respiratory diseases, blood & lymphatic, infection and vascular.

Laboratory findings

During clinical studies, mean values for haemoglobin and haematocrit gradually decreased but remained within the reference range. White blood cells remained within normal limits for ET patients throughout the study. Cases of thrombocytopenia were reported in all studies with an incidence varying from 1% to 2.7%.

Clinical laboratory parameters including liver and renal function tests remained within normal limits for the duration of the study.

Concomitant medications

During the study 13 970-301, concomitant medications were taken by 79.9% of patients overall. Many patients received concomitantly cytoreductive drugs and anagrelide: hydroxyurea was taken by 31.6% of patients overall (24.8% in the ET group and 42.4% in the non-ET group), interferon by 4% and busulfan by 3.3%. Aspirin was the second most common concomitant medication (26.3%). It should be noted that a comparison of prior and concomitant medications shows a large rise in the use of acetaminophen (from 1.8% to 9.3%). Other frequently taken medications were furosemide, allopurinol, ranitidine, digoxin.

Post-marketing experience

Anagrelide was first granted a marketing authorisation in the USA in March 1997 for essential thrombocythaemia (ET) and subsequent approvals for polycythaemia vera (PV), chronic myeloid leukaemia (CML) and all other myeloproliferative disorders (MPDs). It is approved in 11 other countries and until approval in the EU was available in 29 countries on a named patient / compassionate use programme.

From March 1997 to January 2003, the global patient-years exposure is estimated to be in excess of 60000 patient years.

Since the product was marketed in 1997, there have been worldwide a total of 570 patient cases reported globally (healthcare professional and consumer reports) with a total of 1174 events, i.e. on average over 2 events per case. The majority of the events were considered by the reporters as to be related to anagrelide and 47% were serious.

Analysis of the post-marketing data reveals that body system group in with the largest number of reported events is cardiac disorders (16.1%) with the most common events being palpitations, congestive heart failure, tachycardia and myocardial infarction; the majority of these events (excluding palpitations) were serious. The nervous system disorders is the second most common group (13.1%) with the most commonly reported adverse events of headache, often considered as serious; cerebral infarction and transient ischaemic attacks were also noted. The third most common body system group is gastrointestinal disorders (11.4%) with adverse events of diarrhoea, nausea abdominal pain and pancreatitis (14 cases, all considered serious). The body system group investigations (11.3%) refer to laboratory analysis events such as blood creatinine increased, haematocrit or haemoglobin decreased, liver function test abnormal. Renal failure and renal impairment were also reported as serious, in 0.7% and 0.3% of patients respectively. The other body system demonstrating a frequent occurrence of adverse events is respiratory disorders (8.7%) with dyspnoea, pleural effusion, cough and lung infiltration. It should be noted that three cases of pericardial effusion and nine cases of pleural effusion have been reported since anagrelide was marketed. Females experienced more adverse events than males, but this may reflect the population receiving the drug (higher incidence of ET in females: versus males). There were more serious adverse

events reported in the elderly group (>65 years, for both males and females) than in the younger patients as would be expected.

Two cases involving exposure of anagrelide in pregnancy was recorded. In the first case the patient, 36 years old, was receiving anagrelide during the first 8 weeks and 6 days of pregnancy. She experienced pre-eclampsia and baby was delivered by caesarean section at 32 weeks. The baby developed necrotising enterocolitis and thrombocytopenia ($17 \times 10^9/L$), requiring platelet support. Platelet count normalised and no further transfusions were required. The reporter did not provide a causality for the two events in relation to anagrelide. In the second case, the patient whose age was unknown had been receiving anagrelide for 2 months when she discovered she was 6 weeks pregnant. No additional outcome information is available.

One patient diagnosed with a myeloproliferative disorder (not specified) experienced acute leukaemia. He had been treated previously with hydroxyurea.

16 deaths were reported during the reporting period: 1 death is related to anagrelide (progressive dyspnoea with lung cancer), 4 deaths are possibly related (arrhythmia, cerebral haemorrhage, renal failure) and 8 are not assessed; the 3 other cases are regarded as not related.

Safety information from ATU

It is to be noted that among all 451 patients included in the cohort ATU, only 13 cases of serious adverse events were reported. The only reported case of death concerned a patient who presented a rhabdomyolysis, from which he recovered, but died 3 weeks later due to ischemic cardiac insufficiency. This case was considered as serious and unexpected.

Another patient developed an allergic reaction 20 days after the start of Xagrid, treatment was stopped and the patient recovered. This case can be considered as serious unexpected.

The most frequently reported cases concerned cardiovascular effects (96 cases) with palpitations (33/96), Myocardial infarction (18/96) and cardiac failure (19/96). 67 cases were reported under Nervous system disorders (headache and migraine mostly reported (34/67)). There were 14 cases of pancreatitis among the 51 cases reported under gastro-intestinal system disorder. Further, 8 cases of pulmonary hypertension were reported under vascular system disorders among 32 cases.

It should be highlighted that the collection of safety information from ATU in France was still ongoing at the time of approval and such information is reported to the authorities on a regular basis.

Safety information from the MRC PT1 study

The MRC PT1 study is an ongoing randomised controlled trial (non-GCP and not sponsored by the applicant). This is a three armed study: the high risk ET patient arm compares anagrelide plus aspirin versus HU plus aspirin with a long-term planned follow-up: PT1 (Primary Thrombocythemia Trial – Medical Research Council UK 1997 – a long-term active comparator randomised controlled trial in patients with risk stratified ET).

Primary objectives (in high-risk patients) were to compare the effect of hydroxyurea and anagrelide on the incidence of vascular events, and to compare the efficacy of hydroxyurea and anagrelide in terms of reducing elevated platelet counts.

Secondary objectives (in intermediate- and high-risk patients) were to establish whether each treatment modality alters the risk of leukaemic or myelofibrotic transformation.

It was initially proposed to include as many patients as possible including previously diagnosed patients regardless of whether or not they had received treatment previously. High-risk patients were defined as ET Patients having any of the following features:

- Age ≥ 60 years
- Platelet count $> 1000 \times 10^9/l$ (current or previous)
- History of ischaemia, thrombosis or embolic events (including erythromelalgia)
- Haemorrhage considered to be related to PT

- Presence of hypertension or diabetes

Since low-dose aspirin has been shown to reduce minor ischaemic symptoms in patients with thrombocythaemia, it was decided to administer aspirin to both arms. This group of high-risk patients was randomised into 2 further arms: aspirin (75 mg) + hydroxyurea (407 patients) *versus* aspirin (75 mg) + anagrelide (0.5 mg twice daily) (408 patients). Recruitment commenced in July 1997 and was closed in August 2002. A total of 815 high-risk patients entered the study.

In September 2003, the CPMP received information that the anagrelide plus aspirin arm of the MRC PT1 trial had been discontinued, following findings of progressive myelofibrosis and thrombohaemorrhagic events.

A preliminary analysis of these data (from the high-risk group) revealed an excess of serious adverse events in the anagrelide arm. These events included a small number of patients (6 of a total of 400 ET patients) who have shown progressive myelofibrosis. Preliminary analysis has also revealed an excess of patients with cardiovascular (17 patients in the anagrelide arm vs 9 patients in the hydroxyurea arm) and haemorrhagic (21 patients in the anagrelide arm vs 8 patients in the hydroxyurea arm) events, though survival between the 2 arms of the trial showed no difference. The differences between the two treatment arms were not statistically significant. Overall cardiovascular events, as observed in the MRC PT1 trial, occurred in 5% of patients in the hydroxyurea arm vs 7% in the anagrelide arm. Further data from the MRC PT1 study will be reviewed in November 2004 as part of the annual review by the MRC Leukaemia Trials Steering Committee.

Discussion on clinical safety

Overall anagrelide has been administered in clinical trials to 4 600 patients during a period from 1988 to 1997. The safety of anagrelide has been examined in 4 open label clinical studies. In 3 of the studies (700-012, 700-014 and 700-999), 942 patients who received anagrelide at a mean dose of approximately 2mg/day were assessed for safety. In these studies 22 patients received anagrelide for up to 4 years. The safety data submitted by the company are mainly based on the study 13 970-301 which is the largest of all of the studies in terms of number of patients and length of exposure. In the latter study 3660 patients who received anagrelide at a mean dose of approximately 2mg/day were assessed for safety. In this study 34 patients received anagrelide for up to 5 years. Confirmed start dates of therapy were only available for 3027 patients (the 'defined' safety population) and parameters involving exposure time have been based on this subset of patients. 544 of the patients from studies 700-012, 700-014 and 700-999 were transferred into study 13970-301, 529 of which were included in the safety population, lack of information preventing the inclusion of the remaining 15 patients.

It must be noted that many patients withdrew from studies (38.3% discontinued and 61.7% were lost to follow-up). Finally only 34/3027 patients received anagrelide during five years with only 21 in the ET indication. The high percentage of patients who discontinued due to an AE (23.1%) is a concern since ET is a chronic disease and drugs used to treat it are supposed to be given on long-term basis.

Anagrelide as Agrylin has been available as a marketed product in the USA since March 1997 and via a named patient or compassionate use programme in EU. From March 1997 to January 2003, the global patient-years exposure is estimated to be in excess of 60000 patient years. The safety data provided by the post-marketing reports confirm the safety profile that had been made during the clinical trials.

In order to provide further reassurance for the use of anagrelide in the proposed indication, the applicant performed analyses of the available European Compassionate use data to support the dose, the efficacy and safety of Xagrid. The applicant provided data on e.g. 451 ET patients who are currently treated with anagrelide through a Compassionate Use Programme (ATU or Temporary Authorisations for Use). Most of them correspond to the indication, which is the scope of this MAA (this Compassionate Use Programme only included ET patients at risk who are resistant, refractory, or

intolerant to hydroxyurea). The review did not identify any new safety issues with regard to anagrelide other than one confirmed case of rhabdomyolysis possibly related to anagrelide.

In total 601 deaths are reported in the MAA, in the ET population 197 patients (8,8%) died in study 13,970-301 and another 10 deaths were reported in the other clinical trials. Taking the ET population as a whole, a total of 25 treatment-related deaths occurred out of a total population of 2654, yielding an incidence of 0.9%. In absence of controlled data, a comparison with the standard population indicates that the overall number of deaths reported in the ET population is expected. The cause of death was provided in 18 out of the 25 treatment related cases. The majority of deaths were due to cardiovascular disease (8/18) with the remainder dying from a variety of causes including pulmonary disease, CVA, lymphoma and multi-organ failure. Finally, the cause of death was unknown in 8 cases. However, there are no unexpected findings in the ET population as a whole (related and unrelated deaths).

Thrombosis and haemorrhage are a major cause of morbidity and mortality in patients with ET. Those over 60 years of age, a history of thrombosis or ischemic events and platelet counts over $1000 \times 10^9/l$ are considered to be at highest risk. Many patients in the anagrelide clinical studies would fall within this high-risk category.

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 phosphodiesterase III). Gradual dose titration may help diminish these effects.

The applicant has provided safety data presented by age and disease. The overall AE/SAE incidence rates for the >65 years of age group are slightly higher when compared to the data presented on the 18 to <60 group. The incidence of SAEs were twice as high in the older patient population. In the older patients, the most commonly recorded SAE was congestive cardiac failure. Therefore, anagrelide should be used with caution in this population. The safety data in elderly clearly shows the need for further analysis of this patient group. The lack of comparative data is considered a drawback.

With reference to the issue of leukaemic transformation, a review of the clinical safety database has shown no increased risk of transformation to acute leukaemia or myelodysplastic syndrome in patients that have received anagrelide for up to 7 years. It should be pointed out however that this is quite a short term.

Of 2654 ET patients from studies 700-012, 700-014, 700-999 and 13970-301, 54 (2.0%) patients transformed to acute leukaemia/myelodysplasia. However, a majority of these patients had received cytoreductive therapy before anagrelide. Only 1 of 390 (0.3%) of ET patients who had not received cytoreductive therapy recorded a transformation to acute leukaemia/myelodysplasia.

The above seems to support the possibility that treatment with cytoreductive agents results in a higher incidence of leukaemic transformations in patients diagnosed with ET.

Nevertheless, the potential occurrence of leukaemic transformations should be carefully monitored post-marketing.

Cases of cardiomegaly and congestive heart failure have been reported with use of anagrelide and are considered to be uncommon “real” effects. In ET patients who have a high risk of cardiovascular complications due to the disease, it is still difficult to establish a possible link between observed cardiovascular effects and direct toxic effect of Xagrid.

A preliminary analysis of the data from the high-risk group of the MRC PT1 study revealed an excess of serious adverse events in the anagrelide arm. These events included a small number of patients (6 of a total of 400 ET patients) who have shown progressive myelofibrosis. Preliminary analysis has also revealed an excess of patients with cardiovascular (17 patients in the anagrelide arm vs 9 patients in the hydroxyurea arm) and haemorrhagic (21 patients in the anagrelide arm vs 8 patients in the hydroxyurea arm) events, though survival between the 2 arms of the trial showed no difference.

Overall cardiovascular events, as observed in the MRC PT1 trial, occurred in 5% of patients in the hydroxyurea arm vs 7% in the anagrelide arm.

Although, the differences between the two treatment arms were not statistically significant, it should be noted that these are small patient numbers and the clinical significance rather than the statistical significance should be considered when discussing this safety concern.

Anagrelide should be used with caution in patients of any age with known or suspected heart disease, and only 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.

The potential cardiovascular risk associated with the use of anagrelide should be carefully monitored post-marketing and includes: vasodilatation; tachycardia; palpitations; congestive heart failure; decrease in blood pressure; cardiomegaly and myocardial infarction.

Anagrelide is an inhibitor of cyclic AMP phosphodiesterase III (PDE III). Therefore, concomitant use of anagrelide with other phosphodiesterase (PDEIII) inhibitors such as milrinone, amrinone, enoximone, olprinone and cilostazol is not recommended. The potential risks and benefits of the concomitant use of anagrelide with acetylsalicylic acid in patients with a platelet count greater than $1500 \times 10^9/l$ and/or a history of haemorrhage should be assessed before treatment is commenced. Potential interactions are adequately addressed in the SPC.

There are only limited data available on the use of anagrelide in the paediatric population and anagrelide should be used in this patient group with caution.

Further, there are no adequate data from the use of anagrelide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown and the use of Xagrid during pregnancy is not recommended. Mothers should discontinue breast-feeding when taking Xagrid.

Currently, there are no specific data available in patients with impaired renal function and/or hepatic function. The potential risk and benefits of anagrelide therapy in these patients should be assessed before treatment is commenced and doses are to be titrated on an individual patient basis. Hepatic metabolism represents the major route of drug clearance and liver function may therefore be expected to influence this process although no specific dosage recommendations can be made. Due to the lack of data, Xagrid is contraindicated in patients with severe hepatic and/or renal impairment.

The applicant has committed to undertake an open label, single dose, phase 1 study to compare the pharmacokinetics and tolerability of anagrelide in healthy subjects and subjects with severe renal impairment and subjects with moderate hepatic impairment.

The safety issues identified during clinical trials and post-marketing experience have been appropriately addressed in the SPC and Package Leaflet. Furthermore, the safety points identified will be closely monitored by the applicant in future PSURs - possible cardiovascular toxicity (myocardial infarction, cardiac failure), possible malignancies as cases of transformation to acute leukaemia or myelodysplasia (independently of spontaneous transformation due to the disease), rare cases of pancreatitis, gastro-intestinal haemorrhage, lung infiltration, myalgia/rhabdomyolysis, cutaneous reactions such as bullous reaction, and finally few cases of pulmonary hypertension. These issues and in particular mortality, cardiovascular events (including possible cardiomyopathy), acute leukaemia and follow-up of pregnancies occurring while the patient is being treated with anagrelide, will also be further addressed in a Post Authorisation Safety Study (PASS) in the EU. After 5 years of follow-up the study may be continued for an additional 5 years to obtain specific information on pregnancy outcomes and follow-up in women of childbearing potential, as well as haematological transformations. This study will compare long-term safety data of a cohort of Essential Thrombocytopenia patients, on Xagrid and on other treatment strategies. Secondary objectives are efficacy and utilisation analysis.

No comparative trial was performed with Xagrid and this omission could be considered as adequately justified by the applicant, mainly due to ethical reasons and accumulated experience. However, in order to provide further complementary data on long-term safety and efficacy, in particular to elucidate the potential cardiovascular risk associated with anagrelide, the applicant will conduct a randomised clinical trial comparing the efficacy and safety of anagrelide and hydroxyurea as a post-marketing commitment.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Anagrelide has been demonstrated to be a platelet-lowering agent showing selectivity for megakaryocytes. Its mechanism of action appears to be through primary inhibition of TPO/c-mpl receptor-mediated events in megakaryocytes leading to reduced maturation of the megakaryocytes and ultimately reduced platelet numbers.

The most important adverse effects identified in the pre-clinical safety evaluation programme consist of effects on the cardiovascular and the reproductive systems. Anagrelide has been shown to have positive inotropic and chronotropic activity, and to act as a peripheral vasodilator. These actions are very probably due to inhibition of CAMP phosphodiesterase in cardiac and vascular muscle. There is no evidence of prolongation of QT interval by anagrelide itself, and because of lack of *in vivo* effects, the slow onset inhibition of HERG current at high *in vitro* concentrations of the main metabolite are not considered as clinically relevant.

The significant potentiation by anagrelide of the anti-coagulating effect of heparin in the rat and of cardiovascular responses to a calcium channel blocker *in vitro* suggests a potential for drug interactions with these agents, but such interactions have not been highlighted in patients who received these drugs concomitantly.

Because of the potential harm to the foetus, anagrelide should be used in pregnancy only when the benefit to the mother justifies the potential risk to the foetus. It is not known if anagrelide is excreted in milk, but because of the potential adverse effects to nursing infants it is recommended that either breast-feeding is discontinued or drug treatment is stopped. This is sufficiently discussed in the SPC. Anagrelide is not genotoxic and after careful review of the available evidence deemed to have a low carcinogenic potential. However, in order to substantiate the absence of leukaemogenic potential of anagrelide as compared to the conventional therapy (hydroxyurea), the applicant should have provided more data on the underlying mechanism of this phenomenon. The applicant has committed to undertake a 2-year rat carcinogenicity study with anagrelide post-marketing in order to further elucidate any potential leukaemogenicity of the product.

Efficacy

The goal of treatment in patients with ET is to reduce the platelet count and subsequently to prevent and reduce the incidence of thrombo-haemorrhagic complications. Although no comparative trial was performed (this omission could be considered as adequately justified mainly due to ethical reasons and accumulated experience), activity of anagrelide has been demonstrated in decreasing platelet count in ET patients. 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. The duration of the studies provided was up to 5 years and there is extensive clinical experience since anagrelide has been marketed in USA since 1997, and was

available in the EU for compassionate use. Anagrelide is considered by experts within the field of haematology to compare favourably to other available cytoreductive agents, which are not platelet-selective agents, which are not always well tolerated, and can induce treatment failures.

The number of reports of ET symptoms related to thrombocythaemia (thrombotic, haemorrhagic or vasomotor symptoms) decreased during treatment with anagrelide, corresponding to the decrease in mean platelet count over time on treatment, particularly after the first month of treatment. However, clinical benefit in terms of thrombohaemorrhagic events has not yet been convincingly demonstrated.

Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia 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 essential thrombocythaemia patient is defined by one or more of the following features: >60 years of age; or platelet count $>1000 \times 10^9/l$; or a history of thrombo-haemorrhagic events. Treatment with Xagrid capsules should be initiated by a clinician with experience in the management of ET.

In order to provide further complementary data on long-term safety and efficacy the applicant will conduct a randomised clinical trial comparing the efficacy and safety of anagrelide and hydroxyurea as a post-marketing commitment.

Safety

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 phosphodiesterase III). Gradual dose titration may help diminish these effects.

In study 13970-301 a total of 25 treatment-related deaths occurred out of a total population of 2654, yielding an incidence of 0.9%. In 18 out of the 25 cases the cause of death was identified. The majority of deaths were due to cardiovascular disease (8/18) with the remainder dying from a variety of causes including pulmonary disease, CVA, lymphoma and multi-organ failure. Anagrelide should be used with caution in patients of any age with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks. Anagrelide is an inhibitor of CAMP 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.

Although a review of the clinical safety database has shown no increased risk of transformation to acute leukaemia or myelodysplastic syndrome in patients who have received anagrelide for up to 7 years, the potential occurrence of leukaemic transformations should be carefully monitored post-marketing.

The use of Xagrid during pregnancy is not recommended and mothers should discontinue breast-feeding when taking Xagrid. Further, the potential risk and benefits of anagrelide therapy in patients with impaired renal and/or hepatic function should be assessed before treatment is commenced and doses are to be titrated on an individual patient basis.

The safety issues identified during clinical trials and post-marketing experience have been appropriately addressed in the SPC and Package Leaflet. Furthermore, the applicant will closely monitor the safety points identified in future PSURs and in a Post Authorisation Safety Study (PASS) in the EU which will focus especially on cardiovascular events, acute leukaemia and follow-up of pregnancies. This study will compare long-term safety data of a cohort of Essential Thrombocytopenia patients, on Xagrid and on other treatment strategies. Secondary objectives are efficacy and utilisation analyses.

In order to provide further complementary data on long-term safety and efficacy, in particular to elucidate the potential cardiovascular risk associated with anagrelide, the applicant will conduct a randomised clinical trial comparing the efficacy and safety of anagrelide and hydroxyurea as a post-marketing commitment.

Benefit/risk assessment

Following the assessment of the supplementary documentation provided by the applicant, a number of key issues regarding clinical aspects of Xagrid treatment were identified that needed to be further addressed. The applicant was asked to provide an overall benefit/risk assessment for the use of Xagrid in the indication which is the scope of this MAA, to provide a detailed protocol for the proposed Post Approval Safety Study (PASS), to give a detailed outline of the strategy and tools chosen to address the potential cardiovascular risk and to appropriately define the “at risk” patients referred to in the SPC. Following the review of the responses provided by the applicant, the CPMP concluded that satisfactory responses had been provided to the majority of these issues. However, a few remaining outstanding issues were identified to be addressed by the applicant at an Oral Explanation before the CPMP:

- The overall benefit/risk assessment;
- The potential cardiovascular toxicity.

An Oral Explanation took place on 24 July 2003 and focused on the benefit/risk assessment of Xagrid. The applicant concluded that the benefit/risk assessment conclusion was favourable for the use of Xagrid in “at risk” ET patients. Further, the applicant stated that the potential cardiovascular toxicity of the drug was mostly mild and reversible and will be closely monitored as part of the Risk Management Programme/ PASS programme.

The CPMP considered that there was an unmet medical need for Xagrid and that the product could be a useful alternative to current platelet lowering therapy. Anagrelide is the first platelet-selective agent for use in the treatment of ET and it is non-cytotoxic and non-genotoxic. It has an inhibitory effect on the megakaryocyte maturation without affecting other cell lines in the bone marrow.

It was noted that the documentation was weak (as revealed in the GCP inspection of study 700-014). However, taking into account the nature of the pharmacological activity the Committee considered that the product had been shown to be efficacious in lowering platelet count. There was a lack of information regarding thrombo-haemorrhagic events as a hard outcome, but further data could be provided as part of the post-authorisation commitments.

Although specific safety concerns had been identified during the evaluation, they were considered sufficiently addressed in the SPC and PL and would be closely monitored in the planned PASS programme, which is included as a specific obligation.

A CPMP Opinion was adopted on 24 July 2003 recommending the granting of a Marketing Authorisation for the Xagrid under exceptional circumstances.

The post-marketing commitments agreed as part of the CPMP Opinion on 24 July 2003 had included a specific obligation to provide efficacy and safety data from the ongoing MRC PT1 trial. However, in September 2003, information was received that the anagrelide arm of the MRC PT1 trial had been discontinued, following findings of progressive myelofibrosis and thrombohaemorrhagic events. The issue was brought to the attention of the CPMP during its meeting on 23-25 September 2003. The European Commission, at the request of the EMEA, put the Standing Committee phase on hold pending the outcome of the CPMP discussion regarding the new safety information.

The applicant provided oral clarifications with reference to the MRC PT1 trial on 23 September 2003. Supplementary information in writing was provided by the applicant on 5 December 2003, 12 March 2004 and 12 May 2004.

Following the review of the clinical study information, the Committee agreed that, as the commitment undertaken by the applicant at the time of the CPMP opinion – to provide additional efficacy and safety results - would not be fulfilled, the applicant should be asked to provide further efficacy and safety data as a post-marketing commitment. An *ad hoc* expert group was convened to discuss the design of the additional study required.

Outcome of CHMP ad hoc expert meeting:

The experts considered that the efficacy and safety profile of anagrelide is acceptable in a second-line indication as recommended by the proposed Xagrid (anagrelide) SPC, in the light of the fact that ET is an orphan condition for which there is an unmet medical need within the EU. The granting of a Marketing Authorisation for anagrelide in second-line was therefore considered acceptable provided that a final protocol for an additional clinical study was agreed with the CHMP. The experts confirmed that the study should be a first-line randomised controlled (vs hydroxyurea) clinical trial in treatment naïve patients with primary focus on safety. Although it was considered that an improved PASS registry might generate answers to some of the concerns raised with reference to long-term safety (thromboembolic events, bleeding and leukaemogenicity), it was considered that potential consequences of the positive inotropic effects of anagrelide could be picked up by a well-designed randomised clinical trial within a reasonable time frame.

In the light of the outcome of the *ad hoc* expert meeting, the CHMP considered that there was no further need for the applicant to address outstanding issues during an oral explanation before the CPMP. Following the discussion within the Committee, the original assessment report, the product information and the post-marketing commitments have been revised. In order to provide further complementary data on long-term safety and efficacy, in particular to elucidate the potential cardiovascular risk associated with anagrelide, the applicant will conduct a randomised clinical trial comparing the efficacy and safety of anagrelide and hydroxyurea as a post-marketing commitment.

Following the review of the submitted documentation, the responses provided at the oral hearings, the final SPC and letter of undertaking, and taking into account the outcome of the *ad hoc* expert meeting, the CHMP agreed that Xagrid has shown efficacy in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy, that is encouraging and may be clinically relevant and that allows a conclusion on an acceptable benefit/risk despite the limited efficacy and safety data available. The CHMP concluded that a marketing authorisation for Xagrid would be granted under exceptional circumstances, subject to fulfilling the non-clinical and quality follow-up measures and clinical specific obligations undertaken by the applicant. The indication for which the medicinal product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive data on the safety and efficacy of the medicinal product. In order to collect additional data, the applicant has committed to complete a number of clinical studies post-authorisation within pre-specified time frames, the results of which shall form the basis of an annual re-assessment of the benefit/risk profile.

Recommendation

”Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk profile of Xagrid for “the reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy”, was favourable and therefore recommended the granting of a marketing authorisation under exceptional circumstances.”