14 December 2017
EMA/63484/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Anagrelide Mylan

International non-proprietary name: anagrelide

Procedure No. EMEA/H/C/004585/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Anagrelide Mylan
Applicant:	Mylan S.A.S 117 Allee des Parcs 69800 Saint-Priest FRANCE
Active substance:	anagrelide hydrochloride monohydrate
International Nonproprietary Name/Common Name:	Anagrelide
Pharmaco-therapeutic group (ATC Code):	OTHER ANTINEOPLASTIC AGENTS, Other antineoplastic agents (L01XX35)
Therapeutic indication:	Anagrelide is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. <u>An at risk patient</u> An at risk essential thrombocythaemia patient is defined by one or more of the following features: • > 60 years of age or • a platelet count > 1,000 x 10^9/l or • a history of thrombo-haemorrhagic events.
Pharmaceutical form:	Capsule, hard
Strengths:	0.5 mg and 1 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	100 capsules

Table of contents

List of abbreviations

AE	adverse event
AGL.hcl.mhy	Anagrelide hydrochloride monohydrate
AR	Assessment report
API	Active pharmaceutical ingredient
ASMF	Active substance master file
CEP	Certificate of Suitability of the EP
CHMP	Committee for Medicinal Products for Human use
CFU	Colony forming units
EC	European Commission
ET	essential thrombocythaemia
EU	European Union
GC	Gas chromatography
GMP	Good manufacturing practice
HDPE	High density polyethylene
HPLC	High performance liquid chromatograph
HPLC-MS/MS	high performance liquid chromatography – tandem mass spectrometry
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals
for IS	internal standard
INN	International Nonproprietary Name
IPC	In-process control
IR	Infrared
ISR	incurred samples reanalysis
KF	Karl Fischer titration
LDPE	Low density polyethylene
LLOQ	lower limit of quantitation (the lowest calibration point)
LOD	Limit of detection
LOQ	analytical limit of quantitation
LT	lower than
NF	National Formulary
NfG	Note for Guidance

NMT	Not more than
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PP	Polypropylene
PSD	Particle size distribution
PVC	polyvinylchloride
PVDC	polyvinylidene chloride
QC	Quality control
RH	Relative humidity
SIF	simulated intestinal fluid
SmPC	Summary of product characteristics
TAMC	Total aerobic microbial count
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total combined yeasts/moulds count
ULOQ	upper limit of quantitation
UPLC	Ultra-high performance liquid chromatography
USP	United States Pharmacopeia
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 6 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Anagrelide Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 July 2016.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC as well as a generic medicinal product as defined in Article 10 (1) and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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

An at risk patient

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

- 60 years of age or
- a platelet count > 1,000 x 109/l or
- a history of thrombo-haemorrhagic events.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC) with regards to Anagrelide Mylan 1 mg, hard capsule.

Generic application (Article 10 (1) of Directive No 2001/83/EC) with regards to Anagrelide Mylan 0.5 mg hard capsule.

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Xagrid instead of non-clinical and clinical unless justified otherwise. The reference medicinal product has been authorised under exceptional circumstances.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Xagrid, 0.5 mg, capsule, hard
- Marketing authorisation holder: Shire Pharmaceuticals Contracts Limited
- Date of authorisation: 16-11-2004

- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/295/001

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xagrid, 0.5 mg, capsule, hard
- Marketing authorisation holder: Shire Pharmaceuticals Contracts Limited
- Date of authorisation: 16-11-2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/295/001

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xagrid, 0.5 mg, capsule, hard
- Marketing authorisation holder: Shire Pharmaceuticals Contracts Limited
- Date of authorisation: 16-11-2004
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/04/295/001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Alar Irs

- The application was received by the EMA on 6 December 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 27 March 2017.

- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 July 2017.
- The Rapporteur circulated the joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2017.
- During the PRAC meeting on 01 September the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 14 September 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 13 November 2017.
- The Rapporteur circulated the joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 November 2017.
- During the meeting on December 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Anagrelide Mylan on 14 December 2017.

2. Scientific discussion

2.1. Introduction

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 0.5 or 1 mg of anagrelide (as hydrochloride monohydrate) as active substance.

Other ingredients are:

Capsule contents: lactose, lactose monohydrate, croscarmellose sodium, povidone (K29/32), microcrystalline cellulose and magnesium stearate.

Capsule shell: gelatin, titanium dioxide and iron oxide black (1 mg capsule only).

The product is available in HDPE bottles with tamper-evident child-resistant polypropylene (PP) closures with desiccant as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of anagrelide hydrochloride monohydrate is 6,7-dichloro-3,5-dihydroimidazo[2,1-b] quinazolin-2(1*H*)-one hydrochloride monohydrate corresponding to the molecular formula $C_{10}H_7Cl_2N_3O \cdot HCl \cdot H_2O$. It has a relative molecular mass of 310.56 g/mol and the following structure:

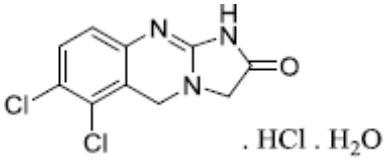


Figure 1: *structure of anagrelide hydrochloride monohydrate*

The chemical structure of anagrelide hydrochloride monohydrate was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry, infrared spectroscopy and x-ray powder diffraction (XRPD).

The active substance is a white to off-white, non-hygroscopic, crystalline powder. It exhibits pH-dependent solubility, being only slightly soluble between pH 3-10.

Although two polymorphic forms are known, the manufacturing process routinely produces the most thermodynamically stable form which is the proposed commercial form. The polymorphic forms can be distinguished by XRPD. No change in polymorphic form was observed at the end of the stability studies under long term and accelerated conditions.

Anagrelide is achiral.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Anagrelide hydrochloride hydrate is synthesized from well-defined starting materials with acceptable specifications. It is considered that enough of the process has been included in the dossier and carried out under GMP such that the fate and purge of impurities can be understood.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

An assessment of potentially genotoxic compounds was carried out *in silico* in line with ICH M7. All of the starting materials and an intermediate gave structural alerts. The purge of these materials is well understood and suitable limits have been set in either intermediates or the active substance in line with published guidance.

The potential for metal contaminants was also assessed. Data shows that metals used in the synthetic process are purged to levels well below the permitted daily exposure (PDE) and so no specific control is deemed necessary.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), identity of chloride counter ion (Ph. Eur.), assay (HPLC), impurities (HPLC, UPLC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur.), and particle size distribution (Ph. Eur.). There is no Ph. Eur. monograph for anagrelide. However, a USP monograph does exist and the specification has been based on that.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Genotoxic impurities are controlled in line with ICH M7.

A test for microbial contamination is not included as no microbes were found in any of the production batches.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5±3 ^{o}C) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. In addition, 9 months' long term data and 6 months' accelerated data was provided from 1 production scale and 2 more pilot scale batches. Samples were tested for appearance, identification, water content, assay and impurities. No significant changes to any of the measured parameters were observed under either set of conditions.

Photostability testing following the ICH guideline Q1B was performed on one pilot scale batch. No changes to any of the measured parameters were observed indicating that the active substance is photostable.

The active substance was exposed to stressed conditions including acid, base and oxidants. Samples degraded under all conditions, more so in the presence of base or acid. The results indicate that the analytical methods, which are also the release methods, are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months at 5±3 ^{o}C in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Anagrelide Mylan capsules contain anagrelide hydrochloride monohydrate, equivalent to either 0.5 or 1 mg of anagrelide freebase. The different strengths are distinguished by colour.

The aim of development was to produce an oral solid dosage form of anagrelide with similar *in vivo* performance to the originator product Xagrid. In the EU, only a 0.5 mg capsule of Xagrid is marketed. However, since the recommended initial posology is 1 mg per day, the applicant developed an additional 1 mg capsule. The formulation is based on that of Xagrid capsules, but without full quantitative knowledge of the various excipients or the active substance polymorphic form. The applicant therefore conducted investigations to compare the proposed product with Xagrid in terms of physical characteristics, dissolution behaviour, impurities content and excipients.

The active substance is a BCS class IV molecule with low solubility and permeability. Accordingly, dissolution rate is likely to impact absorption and thus, particle size of the active substance was investigated in relation to its dissolution rate. A suitable particle size distribution (PSD) was found which affords a similar dissolution profile to Xagrid across the physiological pH range. Accordingly, the active substance is micronized and a suitable limit for particle size is included in its specification, in line with the clinical batch and *in vitro* dissolution data.

Excipients were chosen based on those in Xagrid and include a diluent, binder, lubricant and disintegrant. However, a different disintegrant, (croscarmellose sodium as opposed to crospovidone) was selected. Compatibility of the active substance with the various excipients was demonstrated during stability studies. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Bioequivalence between 1 mg Anagrelide Mylan capsules and 0.5 mg Xagrid capsules was demonstrated clinically. A biowaiver was claimed for the 0.5 mg Anagrelide Mylan capsule since it has the same relative qualitative and quantitative composition as the 1 mg capsule and is produced by the same manufacturer and process. Dissolution profiles for the 0.5 and 1 mg capsules were determined at pH 1, 4.5 and 6.8. At pH 1, complete dissolution occurred within 15 minutes whereas at pH 4.5 and 6.8, profiles were observed to be similar based on f_2 values. Therefore, the biowaiver is acceptable.

The dissolution method selected uses the basket apparatus commonly employed for capsule formulations. Discriminatory power was investigated by comparing standard batches with capsules with meaningful differences in formulation . The method was able to distinguish between batches within the specified time frame.

The primary packaging is an HDPE bottle with tamper-evident child-resistant PP closures with desiccant. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: blending of intra-granular excipients; granulation; drying and milling of granules; blending with extra-granular excipients; encapsulation;

packaging. The process is considered to be a non-standard manufacturing process due to the low content of active substance.

Major steps of the manufacturing process have been validated on production scale using three consecutive batches of common blend used to make 3 batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. In-process controls (IPCs) are carried out. The proposed in-process controls (IPCs) are considered adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance, identification (HPLC, UV), assay (HPLC), impurities (HPLC), dissolution (HPLC) and uniformity of dosage units (Ph. Eur.).

The limits for impurities and assay were tightened during the procedure on the request of CHMP and are now considered acceptable.

A risk assessment was carried out in line with ICH Q3D to determine the likelihood of any elemental impurities being present in the finished product based on contributions from the active substance, excipients, primary packaging and manufacturing equipment. The levels of any elemental impurity potentially present was determined and found to be below 30% of the PDE for all batches tested. Therefore, no limit for specific elemental impurities is included in the specification.

Tests for water content and microbiological contamination were added and subsequently tightened during the procedure at the request of CHMP.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from three production scale batches of both strengths of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for appearance, dissolution, water content, identification, assay, impurities and microbial contamination. The analytical procedures used are stability indicating and are the same (with the same limits) as used for release testing. No significant variability or trends were observed for any of the measured parameters under either set of conditions.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples of 0.5 mg capsules stored outside the primary packaging showed some degradation whereas samples stored within the packaging were stable. The 1 mg capsules were shown to be stable inside and outside the primary packaging.

In-use stability studies were carried out on two batches of 0.5 mg capsules previously stored for up to 18 month under long term conditions. The in-use studies lasted 50 days, i.e. the full in-use shelf-life of the product given that bottles contain 100 capsules and the intended posology is 2 capsules per day. No variability or trends to any of the measured parameters were observed. Nonetheless, given the need for a desiccant in the bottle, the product should be stored in the original bottle in order to protect from moisture.

Based on available stability data, the proposed shelf-life of 36 months without any temperature restriction is acceptable. The 1 mg capsule should be stored in the original package in order to protect from moisture, whereas the 0.5 mg capsule should be stored in the original package in order to protect from light and moisture, as stated in the SmPC (section 6.3).

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The

non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Anagrelide Mylan manufactured by Mylan S.A.S is considered unlikely to result in any significant increase in the combined sales volumes for all anagrelide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

The CHMP considers the non-clinical dossier is acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical dossier is acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing anagrelide hydrochloride monohydrate. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fasting conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Exemption

One bioequivalence study was conducted on the 1 mg capsule strength under fasting conditions. To fulfil the requirements of a biowaiver for lower strength, 0.5 mg hard capsule, dissolution testing was performed.

The waiver is justified, since the following general biowaiver requirements are met:

a) the pharmaceutical products are manufactured by the same manufacturing process

b) the qualitative composition of the different strengths is the same

c) the composition of the strengths are quantitatively proportional

d) appropriate *in vitro* dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Dissolution profiles are considered similar, because more than 85% of the drug substance is dissolved within 15 minutes, or the similarity factor (*f2*) is between 50 and 100.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

A randomized, open-label, single dose, two-period, cross-over, bioequivalence study comparing Anagrelide (as hydrochloride monohydrate) 1 mg hard capsules to Xagrid 0.5 mg hard capsules in healthy volunteers under fasting conditions.

2.4.2. Pharmacokinetics

Methods

Study design

Study was an open-label, laboratory-blinded, randomized, single dose, two-period, two-treatment cross-over bioequivalence study in healthy male and female adult subjects under fasting conditions with a wash out period of 7 days between two administrations. Each study period included a drug administration of either 1 x 1 mg hard capsule of test products or 2 x 0.5 mg hard capsule of the reference product.

Food and fluid intake

Subjects were confined to the clinical facility at least 12 hours prior to drug administration and remained at the study centre until their 8 hrs post-dose blood sample was collected. Study drug was taken orally after a 10-hour overnight fast with 200 ml water. Standard meals were provided at scheduled times, i.e. at 10.5 hrs before and 4 and 6 hrs after the dose. Water was not permitted 1 hour before dosing until 2 hours post-dosing. Subjects were free to drink additional fluids from 4 hrs following the drug administration.

Sampling schedule

17 blood samples were collected for the assessment of Anagrelide in plasma. Blood collections were performed prior to the administration of study medication (0 pre-dose) and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00 and 8.00 hours after study drug administration. Treatments were separated by a washout period of 7 days.

Test and reference products

Test Product: Anagrelide 1 mg hard capsules (equivalent to 1.22 mg of Anagrelide hydrochloride) by Synthon Hispania S.L., Spain; batch No.: 140023; batch size: 100.000 capsules; manufacturing date: Feb 2014, expiry date: Feb 2015

Reference Product: Xagrid 0.5 mg hard capsules by Shire Pharmaceutical Contracts Ltd., UK (manufactured by Wasdell Packaging Limited, UK); Lot No.: A99167A/2 from UK market; expiry date: Sep 2016

Anagrelide Mylan 0.5 mg and 1 mg manufactured by Synthon Hispania S.L Spain (batch No.: 140023, manufacturing date; February 2014, exp. date February 2015) has been compared to Xagrid 0.5 mg manufactured by Wasdell Packaging Limited, UK (Batch No: A99167A/2, exp. date: September 2016).

Populations studied

A total of 44 healthy adult subjects (Caucasian race, aged 19 – 54 years, BMI 20.00 – 29.50, 22 male and 22 female subjects) were included in the study. Only non-smokers were allowed in this study.

43 subjects completed both study phases and were included in the pharmacokinetic and statistical analysis. No major protocol deviations were reported. Inclusion and exclusion criteria were presented and were acceptable for a BE study and for the product under investigation.

Drop outs: Subject No. 18 dropped out due to adverse events (mild restlessness, moderate headache, 2 episodes of vomiting and weakness during the wash-out period of period 1).

Analytical methods

Plasma concentrations of Anagrelide were determined using a validated reversed phase HPLC-MS/MS method. Study drugs were extracted from 50 µl of plasma by protein precipitation. $^{13}C_3D_2$-anagrelide was used as internal standards.

Blood samples were collected into K_2EDTA tubes and centrifuged. The plasma samples were frozen and retained at -20°C until assay.

8 non-zero calibrates and 6 levels of QC samples containing Anagrelide were used. Calibration standards ranged from 0.075 ng/ml to 12.000 ng/ml, LOQ was 0.075 ng/ml. The quality control concentrations were 0.220 (low), 4.000 (medium) and 9.000 (high) ng/ml for study sample analysis. For method validation, additional QC sample levels at 0.075, 1.500 and 12.000 ng/ml were used.

The linear calibration curve calculated by weighted linear regression (weight = 1/c, where c is nominal concentration of the respective calibration sample) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report are presented. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. Composition of analytical runs has been described.

Incurred sample reanalysis was conducted on 131 samples (8.8 % of 1479 samples). 100% (131/131) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

The maximum study sample storage period from first blood draw to last sample analysis was less than 30 days for Anagrelide. The long-term stability of Anagrelide in human plasma covers 91 days at -20°C and at -70°C.

All concentration values below limit of quantification were set as zero for PK analysis.

Reanalysis of study samples: A total of 1479 study samples were analysed in 45 analytical runs. Fifty-five (55 i.e. 3.7 %) samples were re-assayed for analytical reasons (above ULOQ, insufficient response of IS).

Pharmacokinetic variables

Primary variables: C_{max} and AUC_{0-t}.

Pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, residual area, λ_z and $t_{1/2}$ were determined.

Statistical methods

Pharmacokinetic and statistical analyses were performed using Phoenix WinNonlin version 6.3, SAS version 9.2 and MS Excel 2007 software.

PK parameters for each individual were tabulated and graphically presented. Individual AUC parameters were calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Non-parametric analysis of t_{max} was performed on untransformed data. The analysis of variance model included sequence, subject nested within sequence, period and treatment (i.e. drug formulation) as the sources of variance.

Criteria for conclusion of bioequivalence:

The ratio of geometric least squares means with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters C_{max} and AUC_{0-t} were all to be within the 80.00 to 125.00% bioequivalence range.

Results

Table 1 *Pharmacokinetic parameters for Anagrelide (non-transformed values)*

Pharmacokinetic parameter	**Test N=43**		**Reference N=43**	
	arithmetic mean **geometric mean**	**SD** **CV%**	**arithmetic mean** **geometric mean**	**SD** **CV%**
$AUC_{(0-t)}$ (ng*h/ml)	**17.377** 15.026	± 11.231 64.63 %	**16.952** 14.950	± 8.995 53.06 %
$AUC_{(0-\infty)}$ (ng*h/ml)	**17.753** 15.365	± 11.557 65.10 %	**17.332** 15.297	± 9.236 53.29 %
C_{max} (ng/ml)	**6.713** 5.896	± 3.754 55.93 %	**7.076** 6.129	± 3.846 54.35 %
T_{max}* (h)	1.00	0.5 – 2.50	0.83	0.50 – 2.50

AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table 2 *Statistical analysis for Anagrelide (ln-transformed values)*

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV*
$AUC_{(0-t)}$ (ng*h/ml)	100.60 %	92.03 – 109.97 %	24.91 %
$AUC_{(0-\infty)}$ (ng·h/mL)	100.54 %	91.94 – 109.96 %	
C_{max} (ng/ml)	96.16 %	87.28 – 105.96 %	27.19 %
* estimated from the Residual Mean Squares			

Figure 1 *Linear plot of mean plasma concentrations of Anagrelide after administration of Test and Reference formulations (1 mg strength) to healthy subjects (N=43).*

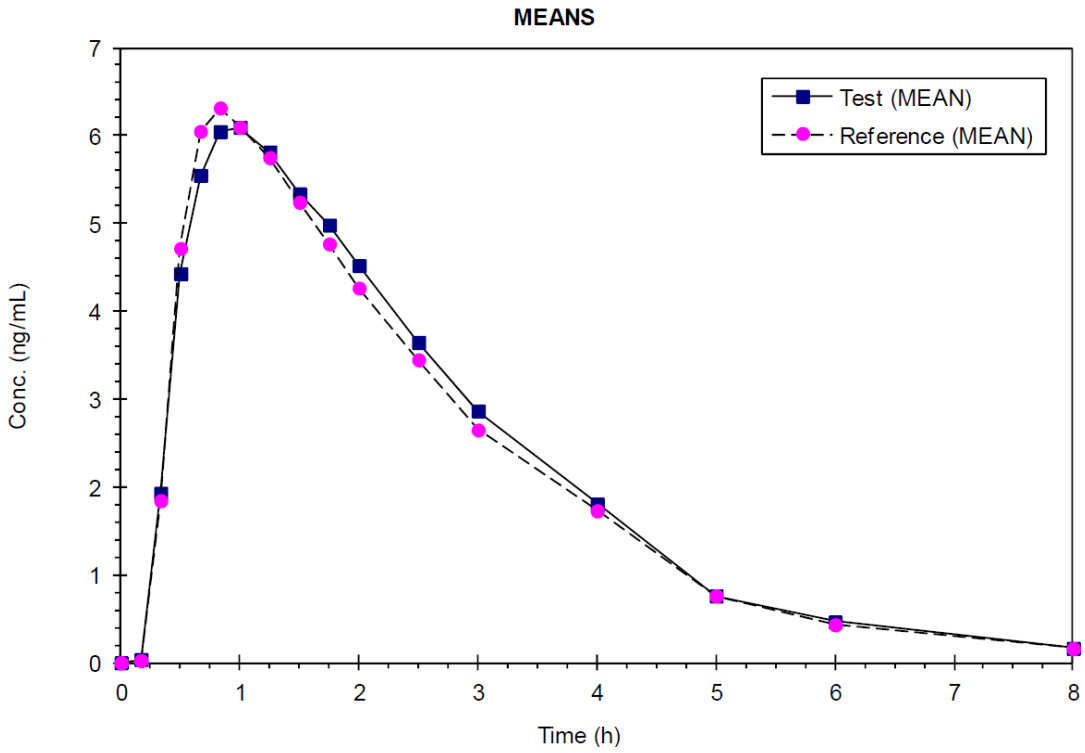
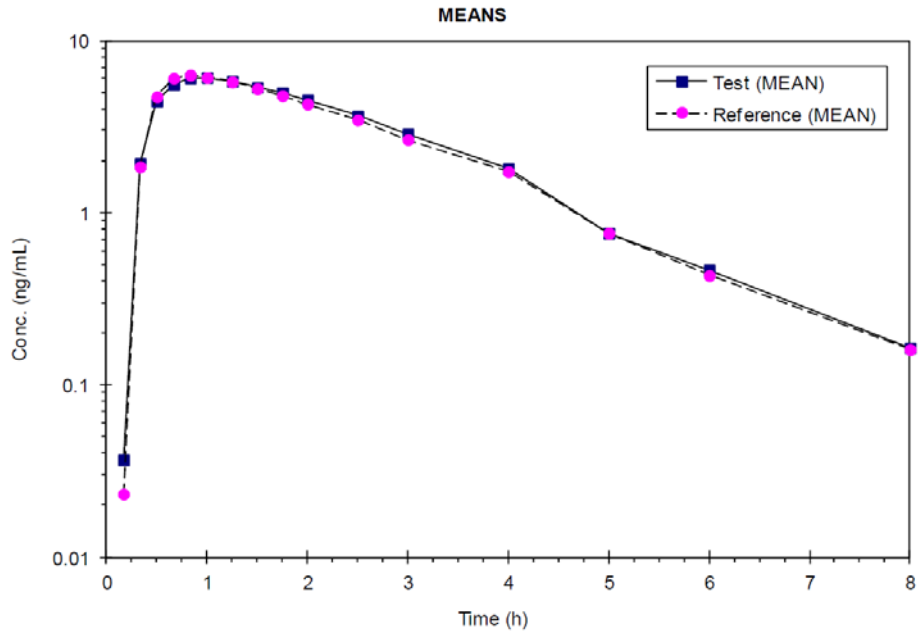


Figure 2 *Semi-logarithmic plots of mean plasma concentrations of Anagrelide after administration of Test and Reference formulations (1 mg strength) to healthy subjects (N=43).*



Safety data

No serious adverse events (AEs) occurred.

Twelve (12) subjects experienced a total of thirty-two (32) mild and five (5) moderate AEs over the course of the study. In total, there were ten (10) mild AEs considered related to the oral administration of Anagrelide 1 mg hard capsules and twenty-two (22) mild and five (5) moderate AEs considered related to the oral administration of Xagrid® 0.5 mg hard capsules.

The most commonly reported AE was “vomiting” reported by 27.9% (n=12) of subjects. Other AEs reported were dizziness (8), headache (7), nausea (5), weakness (2), palpitations (2) and restlessness (1).

Conclusions

Based on the presented bioequivalence study, Anagrelide Mylan is considered bioequivalent with Xagrid.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Cardiac events (QT prolongation, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure) Drug interaction with inhibitors of platelets aggregation (acetylsalicylic acid) Use in patients with moderate or severe hepatic impairment Use in patients with moderate or severe renal impairment (creatinine clearance < 50 ml /min)
Important potential risks	None
Missing information	Use in paediatric population Exposure in pregnancy and lactation Effects on fertility

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient and no additional pharmacovigilance activities are recommended.

Risk minimisation measures

Safety concern	***Routine risk minimisation measures***	***Additional risk minimisation measures***
Important identified risks		
Cardiac events (QT prolongation, ventricular tachycardia, cardiomyopathy, cardiomegaly and congestive heart failure)	SPC sections 4.4, 4.8 and 5.2 Sections 2 and 4 of the PL Product is POM	None
Drug interaction with inhibitors of platelets aggregation (acetylsalicylic acid)	SPC sections 4.5, 4.8 and 5.1 Sections 2 and 4 of the PL Product is POM	None
Use in patients with moderate or severe hepatic impairment	SPC sections 4.2, 4.4 and 4.8 Sections 2 and 4 of the PL Product is POM	None
Use in patients with	SPC sections 4.2, 4.4 and 4.8 Sections	None

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
moderate or severe renal impairment (creatinine clearance < 50 ml /min)	2 and 4 of the PL Product is POM	
Missing information		
Use in pediatric population	SPC sections 4.2, 4.4 and 4.8 Section 2 of the PL Product is POM	None
Exposure in pregnancy and lactation	SPC sections 4.6 Section 2 of the PL Product is POM	None
Effects on fertility	Section 4.6 of the SPC Section 2 of the PL Product is POM	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 4 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic medicinal product containing 0.5 mg anagrelide as well as a

hybrid medicinal product containing 1 mg anagrelide, both referring to the centrally authorised product Xagrid as reference product.

Xagrid is indicated for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk essential thrombocythaemia patient is defined by one or more of the following features: > 60 years of age or a platelet count > 1,000 x 10^9/l or a history of thrombo-haemorrhagic events.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a cross-over design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Anagrelide Mylan met the protocol-defined criteria for bioequivalence when compared with Xagrid. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Anagrelide Mylan is favourable in the following indication:

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

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

- 60 years of age or
- a platelet count > 1,000 x 109/l or
- a history of thrombo-haemorrhagic events.

The originator product was authorised under exceptional circumstances, with the specific obligation of submitting annual literature reviews. The CHMP agreed that this specific obligation should not be imposed on this application for Anagrelide Mylan but annual PSURs (in which literature review will be provided) should be submitted for Anagrelide Mylan, similarly to Xagrid. This would ensure a harmonised assessment across all products.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following

conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.