Public Assessment Report

Decentralised Procedure

Anagrelide 0.5 mg Hard Capsules

(Anagrelide hydrochloride monohydrate)

Procedure No: UK/H/6605/001/DC

UK Licence No: PL 08215/0107

Kent Pharmaceuticals Limited
LAY SUMMARY

Anagrelide 0.5 mg Hard Capsules

(Anagrelide hydrochloride monohydrate)

This is a summary of the Public Assessment Report (PAR) for Anagrelide 0.5 mg Hard Capsules (PL 08215/0107; UK/H/6605/001/DC). It explains how the application for Anagrelide 0.5 mg Hard Capsules was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Anagrelide 0.5 mg Hard Capsules. For ease of reading, the product may be referred to as ‘Anagrelide Capsules’ in this lay summary.

For practical information about using Anagrelide Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Anagrelide Capsules and what are they used for?

Anagrelide 0.5 mg Capsules are a ‘generic’ medicine. This means that Anagrelide 0.5 mg Capsules are similar to a ‘reference’ medicine already authorised in the European Union (EU) called Xagrid (0.5 mg, hard capsules; Shire Pharmaceutical Contracts Limited).

Anagrelide Capsules are used to treat patients with essential thrombocythaemia. This condition occurs when the bone marrow produces too many of the blood cells known as platelets. Large numbers of platelets in the blood can cause serious problems with blood circulation and clotting.

How do Anagrelide Capsules work?

This medicine contains the active substance, anagrelide (as anagrelide hydrochloride monohydrate). Anagrelide interferes with the development of platelets. It reduces the number of platelets produced by the bone marrow, which results in a decrease in the platelet count in the blood towards a more normal level.

How are Anagrelide Capsules used?

The product is available as hard capsules and is taken by mouth (orally).

Anagrelide Capsules can only be obtained with a prescription. The capsules should be taken exactly as advised by a doctor or pharmacist. The patient should check with a doctor or pharmacist if not sure.

The capsules should be swallowed whole with a glass of water. The capsules should not be crushed or the contents of the capsules diluted in a liquid. Anagrelide Capsules can be taken with food or after a meal or on an empty stomach. It is best to take the capsules at the same times every day.

The number of Anagrelide Capsules that patients take can be different, and this depends on the patient’s condition. The patient’s doctor will prescribe the best dose for the patient.

The patient should not take more capsules than the doctor has recommended.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

What benefits of Anagrelide Capsules have been shown in studies?

As Anagrelide Capsules are a generic medicine, studies have been limited to tests to determine that Anagrelide Capsules are bioequivalent to the reference medicine Xagrid (0.5 mg, hard capsules; Shire...
Anagrelide 0.5 mg Hard Capsules

Pharmaceutical Contracts Limited, UK). Two medicines are bioequivalent/therapeutically equivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Anagrelide Capsules?**

Because Anagrelide Capsules are a generic medicine and comparable to the reference medicine Xagrid 0.5 mg, hard capsules (Shire Pharmaceutical Contracts Limited, UK), the possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Anagrelide Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

**Why are Anagrelide capsules approved?**

It was concluded that, in accordance with EU requirements, Anagrelide Capsules have been shown to have comparable quality and to be bioequivalent to Xagrid (0.5 mg, hard capsules; Shire Pharmaceutical Contracts Limited, UK). Therefore, the view was that, as for Xagrid (0.5 mg, hard capsules; Shire Pharmaceutical Contracts Limited, UK) the benefits of Anagrelide Capsules outweigh their risks; and the grant of a Marketing Authorisation was recommended.

**What measures are being taken to ensure the safe and effective use of Anagrelide Capsules?**

A Risk Management Plan has been developed to ensure that Anagrelide Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Anagrelide Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Anagrelide Capsules**

Ireland and the UK agreed to grant a Marketing Authorisation for Anagrelide Capsules on 21 February 2018. A Marketing Authorisation was granted in the UK to Kent Pharmaceuticals Limited on 20 March 2018.

The full PAR for Anagrelide Capsules follows this summary.

For more information about treatment with Anagrelide Capsules, read the package leaflet available on the MHRA website or contact your doctor or pharmacist.

This summary was last updated in May 2018.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

I Introduction Page 5
II Quality aspects Page 6
III Non-clinical aspects Page 8
IV Clinical aspects Page 9
V User consultation Page 10
VI Overall conclusion, benefit/risk assessment and recommendation Page 11
Annex 1 - Table of content of the PAR update for MRP and DCP Page 13
Scientific Discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK considered that the application for Anagrelide 0.5 mg Hard Capsules (PL 08215/0107; UK/H/6605/001/DC) could be approved. The product may be referred to as ‘Anagrelide Capsules’ in this scientific discussion.

Anagrelide Capsules are a Prescription Only Medicine (POM) and are 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 having one or more of the following features:

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

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State.

The application for Anagrelide 0.5 mg Hard Capsules was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the originator medicinal product, Xagrid (0.5 mg, hard capsules; Shire Pharmaceutical Contracts Limited), which was authorised in the EU on 16 November 2004 via the Centralised procedure (EU/1/04/295/001).

The active substance, anagrelide (as anagrelide hydrochloride monohydrate), is an inhibitor of cyclic AMP phosphodiesterase III. It inhibits platelet formation. 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.

One bioequivalence study, comparing the applicant’s test product Anagrelide 0.5 mg hard capsules with the reference product Xagrid 0.5 mg hard capsules (Shire Pharmaceutical Contracts Limited) under fasting conditions, was submitted to support the application. It is stated that the the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that this was a generic application of an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted references to EudraGMDP as certification that acceptable standards of GMP are in place at those sites.

The UK and Ireland considered that the application could be approved at the end of procedure (Day 210) on 21 February 2018. After a subsequent national phase, a Marketing Authorisation was granted in the UK to Kent Pharmaceuticals Limited on 20 March 2018.
II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a white hard capsule containing white to off-white fine powder.

Each hard capsule contains 0.5 mg anagrelide (as anagrelide hydrochloride monohydrate). The product also contains pharmaceutical excipients in the capsule and capsule shell namely, lactose monohydrate, microcrystalline cellulose, povidone K-30, crospovidone Type A, lactose anhydrous, magnesium stearate, gelatin and titanium dioxide (E171). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in high-density polyethylene (HDPE) bottles, each containing 100 hard capsules and 0.5g silica gel as desiccant, and closed with a child resistant polypropylene cap.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE
Anagrelide hydrochloride monohydrate

INN: Anagrelide hydrochloride
Chemical name: 6,7-Dichloro-3,5-dihydroimidazo[2,1-b]quinazoline-2(1H)-one hydrochloride monohydrate

Structure

\[
\text{Cl} \quad \text{N} \quad \text{N} \quad \text{Cl}
\]

\[
\text{HCl} \cdot \text{H}_2\text{O}
\]

Molecular formula: \( \text{C}_{10}\text{H}_7\text{Cl}_2\text{N}_3\text{O} \cdot \text{HCl} \cdot \text{H}_2\text{O} \)

\( M_r: \) 310.56

Appearance: White to off-white powder.

Solubility: Anagrelide hydrochloride is slightly soluble in dimethyl sulfoxide (DMSO) and in dimethylformamide (DMF).

Polymorphism Anagrelide hydrochloride is not reported to exhibit polymorphism in the literature

Anagrelide hydrochloride monohydrate is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.
Anagrelide 0.5 mg Hard Capsules

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data, complying with the proposed specification, are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, hard capsules, each containing 0.5 mg of anagrelide (as anagrelide hydrochloride monohydrate), which were comparable in performance to Xagrid (0.5 mg hard capsules; Shire Pharmaceutical Contracts Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparative in vitro dissolution profiles have been provided for the product and the reference product. The dissolution profiles were satisfactory.

With the exception of titanium dioxide (E171), all excipients comply with their respective European Pharmacopoeia monographs. Titanium dioxide (E171) is in compliance with the current EU Directive concerning the use of colouring agents.

With the exception of lactose (monohydrate and anhydrous) and gelatin, none of the excipients contain materials of animal or human origin.

The suppliers of lactose (monohydrate and anhydrous) have confirmed that the milk used in the production of lactose (monohydrate and anhydrous) is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the suppliers have confirmed that no ruminant material, other than calf rennet, is used during the production of lactose.

The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning minimising the risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specifications have been provided Certificates of Analysis have been provided for all working standards used.
Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 4 years for the unopened product, with special storage instructions of ‘Do not store above 30°C.’ and ‘Store in the original package in order to protect from moisture.’ has been approved. The product is also labelled with the statement ‘After first opening keep the bottle tightly closed and store at dry conditions.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section IV, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of anagrelide are well known. No new non-clinical data have been submitted for the application and none are required given the clinical study data and the pharmaceutical comparative data that have been submitted.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.3 Pharmacokinetics
No new data have been submitted and none are required for an application of this type. Refer to Section III.1, Introduction, above.

III.4 Toxicology
No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
A Phase I risk assessment is supplied that provides values for $\log_{\text{kow}}$ and estimation for $\text{PEC}_{\text{surfacewater}}$. Anagrelide is not a persistent, bioaccumulating and toxic (PBT) compound, and the refined Fpen (fraction of market penetration) used to calculate an estimate for $\text{PEC}_{\text{surfacewater}}$ suggests that anagrelide would not pose a risk to aquatic environments.

Given that the proposed product will be generic of the innovator product and will replace the current approved products, the impact on the overall environment in terms of increased exposure is limited. The ERA is considered to be complete and is acceptable.
III.6 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of anagrelide is well-known.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder (MAH) has submitted a bioequivalence study to support the application.

With the exception of data from the bioequivalence study detailed in Section IV.2, Pharmacokinetics below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for an application of this type.

IV.2 Pharmacokinetics

In support of the application, the applicant submitted the following bioequivalence study:

A randomised, open-label, single-dose, two-period, crossover, bioequivalence study comparing the test product Anagrelide (as anagrelide hydrochloride monohydrate) 0.5 mg hard capsules versus the reference product Xagrid 0.5 mg hard capsules (Shire Pharmaceutical Contracts Limited, UK) in healthy adult subjects under fasting conditions.

Subjects were administered a single oral dose (0.5 mg) of either treatment with 200 ml of water after a 10-hour overnight fast. Blood sampling was performed pre-dose and up to 8 hours post dose in each treatment period. A washout period of 7 days was kept between each consecutive dosing period. The pharmacokinetic results are presented below:

**Table: Statistical Summary of Comparative Bioavailability of Anagrelide**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intra-Subject C.V. (%)</th>
<th>Geometric LSmeans</th>
<th>Ratio (%)</th>
<th>90% Confidence Limits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>Cmax</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>AUC&lt;sub&gt;T&lt;/sub&gt;</td>
<td>18.4</td>
<td>9434.45</td>
<td>9245.51</td>
</tr>
</tbody>
</table>

*units are pg/mL for C<sub>max</sub> and pg h/mL for AUC<sub>T</sub>*

C<sub>max</sub> maximum plasma concentration

AUC<sub>T</sub> area under the plasma concentration-time curve from time zero to T hours

**Bioequivalence Discussion and Conclusion**

The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80.00% to 125.00% for C<sub>max</sub> and AUC values. Thus, the results support the claim that the applicant’s test product is bioequivalent to the reference product Xagrid 0.5 mg Hard Capsules (Shire Pharmaceutical Contracts Limited, UK), under fasting conditions.

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of anagrelide are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical Efficacy

The clinical efficacy of anagrelide is well-known. No new efficacy data are presented or are required for this type of application.
IV.5 Clinical Safety
No new safety data were submitted and none are required for this type of application. No new or unexpected safety issues arose during the bioequivalence study.

IV.6 Risk Management Plan
The MAH has submitted a Risk Management Plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Anagrelide Capsules.

A summary of safety concerns is listed in the table below:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hypersensitivity to anagrelide or any of the excipients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Use in patients with hepatic impairment</td>
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<tr>
<td></td>
<td>Use in patients with renal impairment</td>
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<td></td>
<td>Risk of serious cardiovascular adverse events</td>
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<tr>
<td></td>
<td>Use in patients with risk factors for prolongation of the QT interval or heart disease</td>
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<tr>
<td></td>
<td>Use in combination with PDE III inhibitors</td>
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<tr>
<td></td>
<td>Use in combination with acetylsalicylic acid</td>
</tr>
<tr>
<td></td>
<td>Use in combination with CYP1A2 inhibitors or drugs metabolised by CYP1A2</td>
</tr>
<tr>
<td></td>
<td>Use in combination with oral contraceptives</td>
</tr>
<tr>
<td></td>
<td>Use in pregnancy or breast-feeding</td>
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<tr>
<td></td>
<td>Use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Misuse</th>
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<tr>
<th>Missing information</th>
<th>Use in the paediatric population</th>
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<tbody>
<tr>
<td></td>
<td>Data on the use in pregnancy or breast-feeding in humans</td>
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<td></td>
<td>Effects on fertility</td>
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</table>

Routine pharmacovigilance and risk minimisation activities are planned for all safety concerns which are considered acceptable.

IV.7 Discussion of the clinical aspects
It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the package leaflet was English.

The results 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.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable.

Anagrelide capsules, in the treatment of raised platelet count reduction in at risk patients with essential thrombocythaemia (ET) who are intolerant to their current therapy, have been available in the EU for more than ten years. Their use is well established with recognised efficacy and acceptable safety.

With regard to the current application, sufficient clinical information has been submitted to support the application. Bioequivalence between the test and reference products has been demonstrated in accordance with the current CHMP guidelines.

The overall benefit/risk assessment is therefore considered to be positive.

The grant of a Marketing Authorisation is, therefore, recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is presented below:
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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