CBG MEB

Public Assessment Report

Scientific discussion

Grenalvon 0.5 mg and 1 mg, hard capsules

(anagrelide hydrochloride monohydrate)

NL/H/3934/001-002/DC

Date: 13 November 2018

This module reflects the scientific discussion for the approval of Grenalvon 0.5 mg and 1 mg, hard capsules. The procedure was finalised on 5 October 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Grenalvon 0.5 mg and 1 mg, hard capsules from Alvogen Malta Operations (ROW) Ltd.

The product 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 ET patient is defined by one or more of the following features:
- >60 years of age or
- a platelet count >1000 x 10^9/l or
- a history of thrombo-haemorrhagic events

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xagrid 0.5 mg hard capsules which has been registered in the EEA by Shire Pharmaceutical Contracts Limited through a centralised procedure (EU/1/04/295) since 16 November 2004.

The concerned member states (CMS) involved in this procedure were Croatia, Poland, and Romania.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC for the 0.5 mg strength, and in accordance with Article 10(3) (hybrid application) for the 1 mg strength as there is no European reference product authorised for the strength of 1 mg that the MAH can refer to as a generic application.

II. QUALITY ASPECTS

II.1 Introduction

Grenalvon is a hard capsule filled with white to off-white powder.

The 0.5 mg strength is a hard capsule with an opaque white body and cap.
The 1 mg strength is a hard capsule with a grey body and cap.

The product contains as active substance 0.5 mg of anagrelide, as 0.61 mg of anagrelide hydrochloride monohydrate.

The hard capsules are packed in high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closures and desiccant.

The excipients are:
Capsule contents - lactose monohydrate, croscarmellose sodium, povidone (K29/32), lactose, microcrystalline cellulose, magnesium stearate
0.5 mg Capsule shell – gelatin and titanium dioxide (E171)
1 mg Capsule shell – gelatin, titanium dioxide (E171) and black iron oxide (E172)

The capsule contents of the two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is anagrelide hydrochloride monohydrate, an established active substance described in the United States Pharmacopoeia (USP). Anagrelide hydrochloride monohydrate is a white to off-white powder. It does not contain any chiral centres and thus it does not exhibit any optical isomers. The active substance is slightly soluble in dimethyl sulfoxide and dimethyl formamide. In aqueous environment the solubility profile is pH dependent. Polymorphic form II is consistently obtained.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
A flow-chart for the manufacturing process has been provided. The five steps are clearly described, the quantities used have been clearly indicated. The micronization process has been described in sufficient detail. The chosen starting materials are sufficiently simple.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the USP, plus additional requirements for small potentially genotoxic impurities, particle size, residual solvents and water content. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for six batches stored at 2-8°C (for three batches 36 months data are available) and 25°C/60% RH (three batches stored for six months). No trends were observed. Based on the data submitted, a retest period could be granted of three years, when stored at 2-8°C.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. An adequate overview of the development of the dissolution method has been provided. Comparative dissolution testing between the test product and the innovator product has been performed at pH 1.2, 4.5 and 6.8. The description of the formulation development is considered adequate. Particle size of the drug substance is critical within ranges. The MAH laid down a three-tier particle size specification.

A bioequivalence study has been performed using the 1 mg test product and two capsules of Xagrid 0.5 mg. To support a biowaiver for the 0.5 mg strength, *in vitro* comparative dissolution test data have been provided for both 0.5 mg and 1.0 mg strengths, at pH 1.0, 4.5 and 6.8. The dissolution results are either similar (f2>50) or dissolution results are >85% in 15 minutes.

Manufacturing process
The manufacturing process is a wet granulation process and consists of mixing, granulation, sieving, drying, milling and capsule filling. The manufacturing process is adequately described. Considering the low drug load, the manufacturing process is recognised as a non-standard process. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Only the proposed manufacturing scale has been validated. Future upscaling of the manufacturing scale size will be submitted with a variation with appropriate validation data obtained per validation protocol. All validation results are considered satisfactory. The conclusion is endorsed that the

manufacturing process and its parameters are capable of consistently producing drug product of desired quality, that the results are consistent meeting the acceptance criteria and that no trends have been observed, and that a high degree of batch to batch reproducibility was observed. The manufacturing process has been well validated.

Control of excipients
The colourants comply with the requirements of the concerning monographs in Regulation (EU) No 231/2012, acceptable. All other excipients comply and are tested in accordance with their respective European Pharmacopoeia (Ph.Eur.) monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, related substances, uniformity of dosage units, and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength rom the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three batches for the 0.5 mg tablets, stored at 25°C/75% RH (36 months data) and 40°C/75% RH (6 months data). The batches were stored in the proposed packaging. All stability results meet the set specifications, and no significant changes are observed. The product is considered as photo-stable. On the basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are: ”Store in the original package to protect from light.”

Stability data have been provided demonstrating that the product remains stable for 50 days following first opening of the container, when tightly closed in order to protect from moisture. In view of the stability studies it is considered that the quality of the anagrelide capsules remains much longer than the in-use period of 50 days. It is therefore accepted that a specific in-use shelf-life is not listed in the SmPC. The general shelf-life claim and storage conditions suffice. The opening of the container does not essentially change the stability behaviour of the product.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided, for lactose monohydrate and anhydrous lactose, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Grenalvon has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Grenalvon is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xagrid which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Anagrelide hydrochloride monohydrate is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Grenalvon 1 mg, hard capsules (Genthon B.V., The Netherlands) is compared with the pharmacokinetic profile of two Xagrid 0.5 mg hard capsules (Shire Pharmaceutical Contracts Ltd, United Kingdom).

The choice of the reference product
The choice of the test and European reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The 0.5 mg and 1 mg capsules of Grenalvon are produced via same manufacturing process, and the same excipients are used in both strengths with a proportional amount. The similarity in dissolution profiles of the 0.5 mg and 1 mg strength has been demonstrated based on the f_2>50 at pH 4.5 and 6.8. At pH 1.2, more than 85% dissolved within 15 minutes for both 0.5 mg and 1 mg strength. A detailed assessment for the dissolution tests is presented. Therefore, as pharmacokinetics of anagrelide is dose proportional, the biowaiver for the 0.5 mg strength can be granted and the result of the bioequivalence study with the 1 mg strength can be extrapolated.

Design
A monocentric, open label, randomised, two-treatment, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male (n=22) and female (n=22) subjects, aged 19-54 years. Each subject received a single dose (1 mg) of one of the two anagrelide hydrochloride monohydrate formulations. Each capsule was orally administered with 200 ml water after an overnight fast for at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6 and 8 hours after administration of the products.

The design of the study is acceptable. The wash-out period of seven days is adequate to avoid any carry-over. No pre-dose level was observed. The sample collection period of 8 hours adequately

covers the elimination of the drug. The sampling scheme is also appropriate, as the sampling is frequent around the expected t_{max} (1 hour).

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject dropped out due to mild restlessness, moderate headache, two episodes of vomiting and weakness during the follow-up period. Therefore, 43 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of anagrelide under fasted conditions.

Treatment N=43	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	17.4 ± 11.2	17.8 ± 11.6	6.7 ± 3.75	1.0 (0.5 - 2.5)
Reference	17.0 ± 9.0	17.3 ± 9.2	7.1 ± 3.85	0.83 (0.5 - 2.5)
***Ratio (90% CI)**	1.01 (0.92 - 1.10)	1.01 (0.92 - 1.10)	0.96 (0.87 - 1.06)	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Grenalvon is considered bioequivalent with Xagrid.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, 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 Grenalvon.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Cardiac events in young patients (aged 50 years and under) • Cardiac events related to Corrected QT Interval (QTc) prolongation and Torsade de Pointes (TdP) • 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	• Benign or malignant neoplasms including myelofibrosis • Interstitial lung disease • Exposure during pregnancy • Lack of efficacy/thrombo-haemorrhagic events
Missing information	• Use in paediatric population • Effects on fertility

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xagrid. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic and hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of two bridging reports making reference to Xagrid 0.5 mg hard capsules (scientific content) and Eplerenone 25 mg and 50 mg film-coated tablets (to confirm that any changes made to the proposed PL due to differences in formulation, pack sizes and the MAH's house style do not affect the readability of the leaflet.). The bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Grenalvon 0.5 mg and 1 mg, hard capsules has a proven chemical-pharmaceutical quality. The 0.5 mg strength is a generic form of Xagrid 0.5 mg; the 1 mg strength is a hybrid form. Xagrid is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Grenalvon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 October 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse