LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Webrix
(afatinib)

SE/H/2329/01-04/DC

This module reflects the scientific discussion for the approval of Webrix. The procedure was finalised at 2024-06-27. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Webrix, 20 mg, 30 mg, 40 mg, 50 mg, Film-coated tablet.

The active substance is afatinib, afatinib dimaleate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EB03.
Afatinib is a potent and selective, irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4. It has been shown that afatinib is active against a number of malignancies including lung, head and neck, and breast cancer.
This application concerns its use in the treatment of patients with NSCLC and activating EGFR-TK mutations.
Treatment with afatinib should be initiated and supervised by a physician experienced in the use of anticancer therapies and should be continued until disease progression or until no longer tolerated by the patient. EGFR mutation status should be established prior to initiation of afatinib therapy.

II.2 General comments on the submitted dossier

The application for Webrix, 20 mg, 30 mg, 40 mg, 50 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and CY, EL as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is GIOTRIF, 20 mg, Film-coated tablet, authorised in the EU since 2013, with Boehringer Ingelheim International GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is GIOTRIF, Film-coated tablet, 50 mg from Germany with Boehringer Ingelheim International GmbH as marketing authorisation holder.

II.3 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP: A statement on the application of appropriate GCP standards in the submitted study has been provided. The clinical and the bioanalytical facilities were inspected by the UK (MHRA) authority in 2021, with one critical finding relating to bioanalytical method validation. The organisation provided corrective and preventive actions in response to the inspection report. These were reviewed by the GCP Inspectorate and were considered acceptable. The bioanalytical facility was inspected by the DK (DKMA) and PT (INFARMED) authorities in 2021, without any critical findings. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of afatinib are well known. As afatinib is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Webrix is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Webrix from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Webrix (afatinib film-coated tablets) with the reference product Giotrif (afatinib film-coated tablets).

Pharmacokinetic properties of the active substance
Absorption:
Following an oral dose of afatinib maximal plasma concentrations occur at approximately 2-5 hours. The pharmacokinetics of afatinib is affected by food, and there are restrictions with respect to food in the SmPC of the originator. Concomitant food (high-fat meal) intake decreases the C_{max} and AUC by 50 and 39 %, respectively and therefore afatinib should be administered on an empty stomach.

Linearity:
The pharmacokinetics of afatinib is non-linear with Cmax and AUC0-∞ values increasing slightly more than proportionally in the dose range from 20 mg to 50 mg.

Elimination:
The effective half-life is 37 hours.

Study 0123-22
Methods
This was a single oral dose, two-treatment, three-period, three-sequence, partial replicate crossover study conducted in 41 healthy volunteers, comparing Webrix, 50 mg, film-coated tablets with Giotrif, 50 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of afatinib were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-72} and C_{max}. The study was conducted between 01 June 2022 and 05 July 2022.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for afatinib, n=34.

Treatment	AUC_{0-72} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**747.5 ± 198.0**	**34.2 ± 9.60**	**5.0 (2.5-7.0)**
Reference	**772.2 ± 190.2**	**34.8 ± 8.84**	**5.0 (0.5-7.0)**
***Ratio (90% CI)**	**97.4 (93.42 - 101.54)**	**98.1 (93.80 - 102.54)**	**-**
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-72} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 20 mg, 30 mg and 40 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Absence of studies with the additional strengths of 20 mg, 30 mg and 40 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the plasma exposure increases more than proportionally with increasing dose over the therapeutic range.

Based on the submitted bioequivalence study, Webrix (afatinib, film-coated tablets) is considered bioequivalent with the reference product Giotrif.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Webrix.

Safety specification
The MAH has submitted the version 0.2 RMP dated 2023-07-14 and proposed the following summary safety concerns:

Important identified risks	− Interstitial lung disease (ILD) − Hepatic impairment − Gastrointestinal perforation
Important potential risks	− Decreased left ventricular ejection fraction (LVEF)/heart failure − Developmental toxicity − Hypersensitivity reactions − Poor survival following off-label use in combination with vinorelbine in breast cancer − Use in combination with chemotherapy
Missing information	− None

Assessor's comment: Having considered the data in the safety specification the assessor agrees that the safety concerns listed by the MAH are appropriate.

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 2023-07-14 is considered acceptable.

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 RMS;
- 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date

The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Webrix, is found adequate. There are no objections to approval of Webrix, from a non-clinical and clinical point of view. Bioequivalence between the test and reference

product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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. The language used for the purpose of user testing the PL 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. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-