OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Public Assessment Report

Name of the Product:

Varlota 25 mg, 50 mg, 100 mg, 150 mg, Film-coated tablets

(Erlotinib hydrochloride)

Procedure number: HU/H/0432/001-004/DC

Marketing authorisation holder: Alvogen Malta Operations (ROW) Ltd .

Date: 9 February 2017

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Varlota 25 mg, 50 mg, 100 mg and 150 mg film-coated tablets. The holder of the marketing authorisation is Alvogen Malta Operations (ROW) Ltd

The active substance is erlotinib. Varlota film-coated tablets contain 25 mg, 50 mg, 100 mg or 150 mg erlotinib (as erlotinib hydrochloride), respectively.

The other ingredients are:
- tablet core: lactose monohydrate, cellulose microcrystalline (E460), sodium starch glycolate type A and magnesium stearate (E470b);
- tablet coat: poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol (E1521), talc (E553b), methacrylic acid copolymer and sodium bicarbonate

Appearance:
- The 25 mg film-coated tablets are white to yellowish, round biconvex, engraved with “25” on one side. The diameter of the tablets is 6.1 mm ± 5%.
- The 50 mg film-coated tablets are white to yellowish, round biconvex, engraved with “50” on one side. The diameter of the tablets is 7.6 mm ± 5%..
- The 100 mg film-coated tablets are white to yellowish, round biconvex, engraved with “100” on one side. The diameter of the tablets is 8.9 mm ± 5%..
- The 150 mg film-coated tablets are white to yellowish, round biconvex, engraved with “150” on one side. The diameter of the tablets is 10.5 mm ± 5%..

The tablets are available in blisters.

The active substance of Varlota film-coated tablets (further on: Varlota) is used to treat cancer by preventing the activity of a protein called epidermal growth factor receptor (EGFR). This protein is known to be involved in the growth and spread of cancer cells.

Varlota is indicated for adults. This medicine can be prescribed to the patients if they have non-small cell lung cancer at an advanced stage. It can be prescribed as initial therapy if the cancer cells have specific EGFR mutations. It can also be prescribed if the disease remains largely unchanged after initial chemotherapy, or if previous chemotherapy has not helped to stop the disease.

This medicine can also be prescribed in combination with another treatment called gemcitabine if the patient has cancer of the pancreas at a metastatic stage.

What Patients need to know before taking Varlota?

Those who are allergic to erlotinib or any of the ingredients of this medicine must not take Varlota.

Warnings and precautions

- Patients who are taking other medicines that may increase or decrease the amount of erlotinib in the blood or influence its effect (for example antifungals like ketoconazole, protease inhibitors, erythromycin, clarithromycin, phenytoin, carbamazepine, barbiturates, rifampicin, ciprofloxacin, omeprazole, ranitidine, St. John's Wort or proteasome inhibitors), should talk to their doctor. In some cases these medicines may reduce the efficacy or increase the side effects of Varlota and the doctor may need to adjust the treatment. The doctor might avoid treating the patient with these medicines while they are receiving Varlota.
- For patients who are taking anticoagulants (a medicine which helps to prevent thrombosis or blood clotting e.g. warfarin), Varlota may increase the tendency to bleed. The doctor will need to regularly monitor the patient with some blood tests.
- For patients who are taking statins (medicines to lower the blood cholesterol), Varlota may increase the risk of statin related muscle problems, which on rare occasions can lead to serious muscle breakdown (rhabdomyolysis) resulting in kidney damage. The doctor must be consulted.
- Patients who use contact lenses and/or have a history of eye problems such as severe dry eyes, inflammation of the front part of the eye (cornea) or ulcers involving the front part of the eye, must tell it to their doctor.

See also below "Other medicines and Varlota".

Patients should consult the doctor if they:

- have *sudden* difficulty in breathing associated with cough or fever because the doctor may need to treat the patient with other medicines and interrupt the Varlota treatment;
- have diarrhoea because the doctor may need to treat the patient with anti-diarrhoeal (for example loperamide);
- have severe or persistent diarrhoea, nausea, loss of appetite, or vomiting, immediately, because the doctor may need to interrupt the Varlota treatment; moreover, may need to treat patient in the hospital;
- have severe pain in the abdomen, severe blistering or peeling of skin. The doctor may need to interrupt or stop the treatment;
- develop acute or worsening redness and pain in the eye, increased eye watering, blurred vision and/or sensitivity to light. The doctor or nurse must be informed immediately as the patient may need urgent treatment (see Possible Side Effects below);
- are also taking a statin and experience unexplained muscle pain, tenderness, weakness or cramps. The doctor may need to interrupt or stop the treatment.

See also section "Possible side effects".

Liver or kidney disease
It is not known whether Varlota has a different effect if the liver or kidneys are not functioning normally. The treatment with this medicine is not recommended for those who have a severe liver disease or severe kidney disease.

Glucuronidation disorder like Gilbert's syndrome
The doctor must treat the patients, who are having a glucuronidation disorder like Gilbert's syndrome, with caution.

Smoking
Patients are advised to stop smoking if treated with Varlota as smoking could decrease the amount of this medicine in the blood.

Children and adolescents
Varlota has not been studied in patients under the age of 18 years. The treatment with this medicine is not recommended for children and adolescents.

Other medicines and Varlota
Patients who are taking or have recently taken any other medicines or might take any other medicines must inform their doctor accordingly.

Varlota with food and drink
Patients must not take Varlota with food. See also section "How to take Varlota".

Pregnancy and breast-feeding
Patients must avoid pregnancy while being treated with Varlota. Those who could become pregnant, must use adequate contraception during treatment, and for at least 2 weeks after taking the last tablet.
If the patient becomes pregnant while she is being treated with Varlota, must inform their doctor immediately. The doctor will decide if the treatment should be continued.
Patients must not breast-feed if they are being treated with Varlota.
Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Driving and using machines
Varlota has not been studied for its possible effects on the ability to drive and use machines but it is very unlikely that the treatment will affect this ability.

Varlota contains a sugar called lactose monohydrate.

Those who have been told by their doctor that they have an intolerance to some sugars, contact the doctor before taking this medicinal product.

How to take Varlota

Patients must always take this medicine exactly as the doctor (or pharmacist) has told them. If not sure, it should be checked with the doctor or pharmacist.

The tablet should be taken at least one hour before or two hours after the ingestion of food.

The recommended dose is one tablet of Varlota 150 mg each day if the patient has non-small cell lung cancer.

The recommended dose is one tablet of Varlota 100 mg each day if the patient has metastatic pancreatic cancer. Varlota is given in combination with gemcitabine treatment.

The doctor may adjust the dose in 50 mg steps. For the different dose regimens Varlota is available in strengths of 25 mg, 100 mg or 150 mg.

What to do if more Varlota has been taken than it should have been?

The doctor must be contacted immediately. The patient may have increased side effects and the doctor may interrupt the treatment.

What to do if taking Varlota has been forgotten?

If the patient miss one or more doses of Varlota, he/she must contact the doctor as soon as possible. Patients should never take a double dose to make up for a forgotten dose.

May taking Varlota by stopped by the patient?

It is important to keep taking Varlota every day, as long as the doctor prescribes it for the patient.

Possible side effects

Like all medicines, Varlota can cause side effects, although not everybody experiences them.

Patients must contact their doctor as soon as possible if suffering from any of the side effects listed below. In some cases the doctor may need to reduce the dose of Varlota or interrupt the treatment:

- Diarrhoea and vomiting (very common: may affect more than 1 out of 10 people). Persistent and severe diarrhoea may lead to low blood potassium and impairment of the kidney function, particularly if the patient receives other chemotherapy treatments at the same time. If the patient experiences more severe or persistent diarrhoea, the doctor must be contacted immediately as the doctor may need to treat the patient in the hospital.
- Eye irritation due to conjunctivitis/ keratoconjunctivitis (very common: may affect more than 1 out of 10 people) and keratitis (common: may affect up to 1 in 10 people).
- Form of lung irritation called interstitial lung disease (uncommon in European patients; common in Japanese patients: may affect up to 1 in 100 people in Europe and up to 1 in

10 in Japan). This disease can also be linked to the natural progression of the medical condition and can have a fatal outcome in some cases. If the patient develops symptoms such as sudden difficulty in breathing associated with cough or fever, they must contact their doctor immediately as they could suffer from this disease. The doctor may decide to permanently stop the treatment with Varlota.

- Gastrointestinal perforations have been observed (uncommon: may affect up to 1 in 100 people). Patients who have severe pain in the abdomen must inform their doctor. The doctor must also be informed if the patient had peptic ulcers or diverticular disease in the past, as this may increase this risk.
- In rare cases liver failure was observed (rare: may affect up to 1 in 1,000 people). If the blood tests indicate severe changes in the liver function, the doctor may need to interrupt the treatment.

Very common side effects (that may affect more than 1 in 10 people):

- Rash which may occur or worsen in sun exposed areas. If the patient is exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable.
- Infection.
- Loss of appetite, decreased weight.
- Depression.
- Headache, altered skin sensation or numbness in the extremities.
- Difficulty in breathing, cough.
- Nausea.
- Mouth irritation.
- Stomach pain, indigestion and flatulence.
- Abnormal blood tests for the liver function.
- Itching, dry skin and loss of hair.
- Tiredness, fever, rigors.

Common side effects (that may affect up to 1 in 10 people):

- Bleeding from the nose.
- Bleeding from the stomach or the intestines.
- Inflammatory reactions around the fingernail.
- Infection of hair follicles.
- Acne.
- Cracked skin (skin fissures).
- Reduced kidney function (when given outside the approved indications in combination with chemotherapy).

Uncommon side effects (that may affect up to 1 in 100 people):

- Eyelash changes.
- Excess body and facial hair of a male distribution pattern.
- Eyebrow changes.

- Brittle and loose nails.

Rare side effects (that may affect up to 1 in 1,000 people): flushed or painful palms or soles (Palmar plantar erythrodysaesthesia syndrome).

Very rare side effects (that may affect up to 1 in 10,000 people):
- Cases of perforation or ulceration of the cornea.
- Severe blistering or peeling of skin (suggestive of Stevens-Johnson syndrome).
- Inflammation of the coloured part of the eye.

How to store Varlota?

This medicine does not require any special storage conditions, but it must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Varlota 25 mg, 50 mg, 100 mg and 150 mg film-coated tablets. The procedure was finalised at 31 August 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

In this Decentralised Procedure application the Reference member state, RMS was Hungary, while the concerned member states, CMSs were as follows:

Procedure number	Strength	CMSs
0432/001	25 mg	Cyprus and Poland
0432/002	50 mg	Cyprus, Estonia, Latvia, Lithuania and Poland
0432/003	100 mg	Bulgaria, Cyprus, Estonia, Iceland, Latvia, Lithuania, Poland and Romania
0432/004	150 mg	Bulgaria, Croatia, Cyprus, Estonia, Iceland, Latvia, Lithuania, Poland and Romania

The application concerned tablets with the active substance erlotinib that has a well-established use with an acceptable level of safety and efficacy.

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Varlota 25 mg, 50 mg, 100 mg, 150 mg film coated tablets. The holder of the marketing authorisation is Alvogen Malta Operations (ROW) Ltd . in the RMS.

The product is indicated as follows:

Non-small cell lung cancer (NSCLC):

- for the first-line treatment of patients with locally advanced or metastatic non- small cell lung cancer (NSCLC) with Epidermal Growth Factor Receptor (EGRF) activating mutations.
- for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease after first- line chemotherapy.
- for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

When prescribing Varlota, factors associated with prolonged survival should be taken into account.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with Epidermal Growth Factor Receptor (EGFR)-IHC negative tumours.

Pancreatic cancer:

Varlota in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

When prescribing Varlota, factors associated with prolonged survival should be taken into account.
No survival advantage could be shown for patients with locally advanced disease.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

The marketing authorisation has been granted pursuant to:

- Article 10(1) of the Directive 2001/83/EC generic application) of the 25 mg, 100 mg and 150 mg strengths,
- Article 10(3) of the former Directive (hybrid application) for the 50 mg strength.

No new pre-clinical and clinical studies (besides the bioequivalence study) were conducted, which is acceptable for this abridged application. No scientific advice has been given to the applicant with respect to this product. The applicant has performed one bioequivalence study to demonstrate similarity of the product with Tarceva® 150 mg film-coated tablets (manufactured by Roche Registration Ltd., UK). Thus, the originator products are Tarceva 25 mg, 100 mg, 150 mg film-coated tablets by Hoffmann-La Roche Ltd /Roche Registration Limited, authorised for marketing since 2005.

II. QUALITY ASPECTS

II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Varlota 25 mg, 50 mg, 100 mg and 150 mg film-coated tablets via a decentralized procedure according to Article 10(1) and 10(3) (the 50 mg strength) of Directive 2001/83/EC (i.e. a generic and hybrid application, respectively). The marketing authorisation holder is Alvogen Malta Operation (ROW) Ltd. The drug product is manufactured by Remedica Ltd., Aharnon Street, Limassol Industrial Estate, 3056 Limassol, Cyprus.

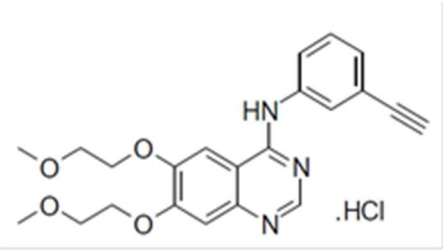
The reference products are Tarceva 150 mg film-coated tablets (containing 150 mg erlotinib hydrochloride as active ingredient) which were the original products of Roche Registration Limited.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

International non-proprietary name (INN): erlotinib hydrochloride.
Chemical name: N-(3-Ethynylphenyl)-[6,7-bis(2-methoxyethoxy)quinazolin-4-yl]amine hydrochloride

Structure:



The active substance is white to off-white crystalline powder; slightly soluble in methanol, practically insoluble in acetonitrile, acetone, ethyl acetate, isopropanol, n-hexane and water. The molecule does not contain any asymmetric carbon atom. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by spectroscopy (FT-IR, UV, ^{1}H-NMR, ^{13}C-NMR), mass spectrometry (MS) and elemental analysis. The discussion of the impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Erlotinib hydrochloride is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the drug substance, which includes the following tests: appearance, identification, chloride identification, loss on drying, sulphated ash, heavy metals, related substances, residual solvents, assay and microbiological purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council on Harmonisation (ICH) Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and satisfactorily validated. Reference materials used by the drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop tablets containing erlotinib hydrochloride as drug substance in 25 mg, 50 mg, 100 mg and 150 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Tarceva 150 mg film-coated tablets, the branded original products of Roche Registration Limited.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the products are shown to be similar to the reference products.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

- 25 mg: white to yellowish, round biconvex, film-coated tablet, engraved with "25" on one side. The diameter of the tablet is 6.1 mm ± 5 %..
- 50 mg: White to yellowish, round biconvex, film-coated tablet, engraved with "50" on one side. The diameter of the tablet is 7.6 mm ± 5 %..
- 100 mg: White to yellowish, round biconvex, film-coated tablet, engraved with "100" on one side. The diameter of the tablet is 8.9 mm ± 5 %..
- 150 mg: White to yellowish, round biconvex, film-coated tablet, engraved with "150" on one side. The diameter of the tablet is 10.5 mm ± 5 %..

The excipients used in the finished product are magnesium stearate, microcrystalline cellulose, lactose monohydrate and sodium starch glycolate Type A and coating mixture (sodium hydrogen carbonate, methacrylic acid – ethyl acrylate copolymer (1:1), type A, macrogol 3350, talc, titanium dioxide E171 and poly(vinyl alcohol)). All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the European Pharmacopoeia on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister and box. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions is approved.

The SmPC, Patient Information (Package) Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their quality and content of the active substance as well as dosage-form characteristics until the end

of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the products. From chemical-pharmaceutical points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamics, pharmacokinetic andtoxicological properties of Erlotinib hydrochloride are well-known. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to erlotinib.

III.2 Pharmacology

Erlotinib is a member of a class of targeted anticancer drugs that specifically inhibits the activity of the epidermal growth factor receptor. The epidermal growth factor receptor (EGFR) autocrine pathway contributes to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis, and metastatic spread. The critical role the EGFR plays in cancer has led to an extensive search for selective inhibitors of the EGFR signalling pathway.

Erlotinib is an orally available EGFR tyrosine kinase inhibitor (TKI) that blocks transduction of propagation signals mediated by the EGFR in a concentration-dependent manner. The epidermal growth factor receptor (EGFR) is overexpressed in many solid tumours.

Erlotinib, a quinazolinamine derivative, acts as a potent and reversible inhibitor of EGFR TK activity. It is in competition with adenosine triphosphate (ATP) for binding to its focused intracellular domain. Erlotinib blocks intracellular auto-phosphorylation of the tyrosine kinase coupled with EGFR. Tyrosine kinase receptors, which are a part of the human epidermal receptor (HER) family, are overexpressed or dysregulated in various types of solid tumours, including non-small-cell lung cancer (40%–80%), colorectal cancer (72%–82%), head and neck cancer (95%–100%), breast cancer (84%–91%), and renal cell cancer (50%–90%). These receptors were therefore recognized as targets for cancer therapy. EGFRs are expressed on the exterior of normal and neoplastic cells. Cancers overexpressing EGFR have a poor response to both chemotherapy and radiation therapy.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

Chronic dosing effects observed in at least one animal species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (liver necrosis), kidney (renal papillary necrosis and tubular dilatation), and gastrointestinal tract (delayed gastric emptying and diarrhoea). Red blood cell parameters were decreased and white blood cells, primarily neutrophils, were increased. There were treatment-related increases in ALT, AST and bilirubin. These findings were observed at exposures well below clinically relevant exposures.

Based on the mode of action, erlotinib has the potential to be a teratogen. Data from reproductive toxicology tests in rats and rabbits at doses near the maximum tolerated dose and/or maternally toxic doses showed reproductive (embryotoxicity in rats, embryo resorption and foetotoxicity in rabbits) and developmental (decrease in pup growth and survival in rats) toxicity, but was not teratogenic and did not impair fertility. These findings were observed at clinically relevant exposures.

Erlotinib tested negative in conventional genotoxicity studies. Two-year carcinogenicity studies with erlotinib conducted in rats and mice were negative up to exposures exceeding human therapeutic exposure (up to 2-fold and 10-fold higher, respectively, based on C_{max} and/or AUC).

A mild phototoxic skin reaction was observed in rats after UV irradiation.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Varlota 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.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamic, pharmacokinetic and toxicological properties of Erlotinib Hydrochloride are well known. As Varlota is a generic and hybrid (change in strength) product there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applicant has not conducted any clinical studies (except the bioequivalence one) with Varlota. All the relevant clinical information provided in the *Clinical overview* is literature based.

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR is expressed on the cell surface of normal cells and cancer cells. In non-clinical models, inhibition of EGFR phosphotyrosine results in cell stasis and/or death.

EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signalling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signalling, the proliferation of cells is stopped, and cell death is induced through the intrinsic apoptotic pathway. Tumour regression is observed in mouse models of enforced expression of these EGFR activating mutations.

One pivotal bioequivalence study (PharOS's study code: 14-064) has been reported in the submitted dossier in order to support essential similarity between Varlota 150 mg film-coated tablets (manufactured by Remedica Ltd., Cyprus for PharOS Generics Ltd., Cyprus) and Tarceva® 150 mg film-coated tablets (manufactured by Roche Registration Ltd., UK) in healthy adult male subjects under fasting conditions according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010).

IV.2 Pharmacokinetics

IV.2.1 Literature data

After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after oral dosing. A study in normal healthy volunteers provided an estimate of the absolute bioavailability of 59%. The exposure after an oral dose may be increased by food.

Erlotinib has a mean apparent volume of distribution of 232 l and distributes into tumour tissue of humans. In a study of 4 patients (3 with NSCLC, and 1 with laryngeal cancer) receiving 150 mg daily oral doses of erlotinib, tumour samples from surgical excisions on day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1185 ng/g of tissue. This corresponded to an overall average of 63% (range 5-161%) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to

an overall average of 113% (range 88-130%) of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95%. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Erlotinib is metabolised in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and 1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib.

There are three main metabolic pathways identified: 1) O-demethylation of either side chain or both, followed by oxidation to the carboxylic acids; 2) oxidation of the acetylene moiety followed by hydrolysis to the aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene moiety. The primary metabolites OSI-420 and OSI-413 of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in non-clinical *in vitro* assays and *in vivo* tumour models. They are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics as erlotinib.

Erlotinib is excreted predominantly as metabolites via the faeces (>90%) with renal elimination accounting for only a small amount (approximately 9%) of an oral dose. Less than 2% of the orally administered dose is excreted as parent substance. A population pharmacokinetic analysis in 591 patients receiving single agent erlotinib shows a mean apparent clearance of 4.47 l/hour with a median half-life of 36.2 hours. Therefore, the time to reach steady state plasma concentration would be expected to occur in approximately 7-8 days.

IV.2.2 Bioequivalence study

The main objective of the study was to prove bioequivalence (to compare the rate and extent of absorption) between Varlota 150 mg film-coated tablets (Test) and Tarceva® 150 mg film-coated tablets (Reference: Roche Registration Limited, U.K.) in healthy, adult, male subjects under fasting conditions. Its design was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study with a suitable washout period between the two periods, in healthy male subjects under fasting condition.

All subjects were fasted (overnight) then administered the Test- and Reference medication (as per the randomisation scheme) as a single oral dose of 1 film-coated tablet containing 150 mg of erlotinib with drinking water during each study period.

Blood samples were taken and plasma concentrations of erlotinib were determined by validated LC-MS/MS method.

The applicant stated that the bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

The pharmaco-kinetic parameters calculated were:

- primary: AUC_{0-t}, C_{max},
- other: T_{max}, $AUC_{0-\infty}$, $t_{1/2}$, K_{el}, extrapolated AUC (in %).

Statistical methods used in the evaluation of bioequivalence were as follows:

- Descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for test (T) and reference (R) pharmacokinetic data.
- Log-transformation of $AUC_{0-\infty}$, AUC_{0-t} and C_{max} data.
- Evaluation of data using a linear mixed-effects model.
- The F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (α=0.05).
- Intra-subject variability of the primary pharmacokinetic parameters were estimated using the root mean square error (RMSE) obtained after carrying out analysis of variance for bioequivalent assessment.
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters.
- Applying non-parametric analysis of T_{max} on untransformed data.
- Descriptive statistics of safety data collected during the whole study period.

Conclusion on bioequivalence studies

Ratio and 90%Confidence Intervals of Test Product versus Reference Product

Erlotinib			
Pharmacokinetic parameter	**Geometric Mean Ratio Test/Ref**	**Confidence Intervals**	**CV %**
$AUC_{(0-t)}$	97.36	87.97 – 107.75%	29.6
C_{max}	102.97	92.91 – 114.11%	30.0

Results derived from analysis of log-transformed primary efficacy parameters (C_{max}, AUC_{0-t}) for erlotinib show that the Test/Reference ratios of least-squares mean values and their 90% confidence intervals are also entirely included within the acceptance range of 80% - 125%. Thus, results support the bioequivalence between the Test- and Reference products.

Based on clinical laboratory assessments, the study medication were found to be safe and well tolerated by all the subjects involved in the study.

Based on the submitted bioequivalence the Varlota 150 mg film-coated tablets (Test) are considered bioequivalent with the Tarceva® 150 mg film-coated tablets (Roche Pharma AG, Germany) (Reference).

Biowaiver

The applicant claimed for biowaiver for the dose strengths of 25 mg, 50 mg and 100 mg on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

a) All strengths i.e. 25, 50, 100 and 150 mg of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The composition of the claimed four strengths (25, 50, 100 and 150 mg) is proportionally similar.
d) In-vitro dissolution data confirm in vivo similarity between the claimed strengths.
e) Erlotinib exhibits linear pharmacokinetics in the claimed therapeutic range (25-150 mg).

The biowaiver claim for the 25 mg, 50 mg and 100 mg dose strengths is acceptable according to the bioequivalence guideline in force (CPMP/EWP/1401/98 Rev.1 and EMA/CHMP/600958/2010/ Corr.*).

The results obtained in this study for the 150 mg strength could be extrapolated to the other claimed strength (25 mg, 50 mg and 100 mg).

IV.3 Pharmacodynamics

No new data have been submitted. No data are required for an abridged application provided bioequivalence has been satisfactorily demonstrated.

IV.4 Clinical efficacy

No new efficacy or safety data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of erlotinib.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the Applicant'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 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	Cutaneous toxicity Interstitial lung disease Liver injury GI fluid loss GI perforation Ocular toxicity Interaction with potent inducers and inhibitors of CYP3A4Interaction with medicinal products that alter pH of the upper gastro-Intestinal (GI) tract Interaction with smoking
Important potential risks	None
Missing information	Pregnancy/lactation Paediatric population Hepatic impairment

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Varlota 25 mg, 50 mg, 100 mg and 150 mg film-coated tablets. However as routine pharmacovigilance activity for the originator, Tarceva guided questionnaires are in place for risks of interstitial lung disease (ILD) and liver injury and the same pharmacovigilance activities are requested from the proposed marketing authorisation holder's for generic versions of erlotinib as well.

Risk Minimisation Measures: similarly to the originator's product, the marketing authorisation holder of Varlota 25 mg, 50 mg, 100 mg, and 150 mg film-coated tablets must issue educational material for healthcare professionals as additional risk minimisation measure for the risk of ILD. The purpose of this material is to enable prescribers to anticipate and manage interstitial lung disease.

All healthcare professionals who are expected to prescribe erlotinib must be provided with an information pack containing the following items:

- SmPC and Package Leaflet.
- Educational material for the healthcare professionals, which contains has the following key elements:
  - ILD-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib (overall incidence of approximately 0.6%). A higher incidence of ILD (approximately 5% with a mortality rate of 1.5%) is seen among patients with Japanese origin.

- Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent.
- In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, erlotinib should be interrupted pending diagnostic evaluation. Patients treated concurrently with erlotinib and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity.
- If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment initiated as necessary

IV.6.3 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.

Currently, no routine PSUR reporting is required for generic products containing erlotinib.

IV.7 Discussion on the clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

To support the application the applicant has adequately demonstrated bioequivalence between Varlota film-coated tablets and the reference product Tarceva 25 mg, 100 mg, 150 mg film-coated tablets.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Varlota 25 mg, 50 mg, 100 mg and 150 mg tablets, generic versions of erlotinib (as hydrochloride, the legal base of the submission of the 50 mg strength was hybrid application, this strength being different from those of the reference product. The future holder of authorisation was Alvogen Malta Operations (ROW) Ltd in the RMS

The reference products were Tarceva 25 mg, 100 mg, and 150 mg film-coated tablets by Hoff-mann-La Roche Ltd /Roche Registration Limited.

The indication was as follows. Treatment of:

Non-small cell lung cancer (NSCLC):

- Varlota is indicated for the first-line treatment of patients with locally advanced or metastatic NSCLC with Epidermal Growth Factor Receptor (EGFR) activating mutations.
- Varlota is also indicated for switch maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations and stable disease first-line chemotherapy.
- Varlota is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

When prescribing Varlota, factors associated with prolonged survival should be taken into account.

No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-IHC negative tumours;

Pancreatic cancer:

- Varlota in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer.

When prescribing Varlota, factors associated with prolonged survival should be taken into account. No survival advantage could be shown for patients with locally advanced disease.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Varlota 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and 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. The language used for the purpose of user testing the patient information 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. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached