Applicant : Eurolab (Pty) Ltd
Proprietary name : Gefirix
Dosage form and strength : Film-coated tablets 250 mg
Approval date : 26 October 2021

APPROVED PROFESSIONAL INFORMATION FOR

GEFIRIX

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

GEFIRIX 250 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **GEFIRIX** film-coated tablet contains 250 mg of gefitinib.

Excipients with known effect:

GEFIRIX contains sugar (lactose).

GEFIRIX contains 163,5 mg of lactose (as monohydrate) per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

GEFIRIX 20 mg: The film-coated tablets are brown, round, biconvex, debossed with “LP100” on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

GEFIRIX is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of Epidermal Growth Factor Receptor Tyrosine Kinase (EGFR-TK) (see section 4.4).

4.2 Posology and method of administration

Treatment with **GEFIRIX** should be initiated and supervised by a medical practitioner experienced in the use of anti-cancer therapies.

Posology

The recommended posology of **GEFIRIX** is one 250 mg tablet once a day. If a dose is missed, it should be taken as soon as the patient remembers. If it is less than 12 hours to the next dose, the patient should not take the missed dose. Patients should not take a double dose (two doses at the same time) to make up for a forgotten dose.

Special populations

Hepatic impairment

Patients with moderate to severe hepatic impairment (Child-Pugh B or C) due to cirrhosis have increased plasma concentrations of gefitinib. These patients should be closely monitored for adverse events. Plasma concentrations were not increased in patients with elevated serum aspartate transaminase (AST), serum alkaline phosphatase or serum bilirubin due to liver metastases (see section 5.2).

Renal impairment

No dose adjustment is required in patients with impaired renal function at creatinine clearance > 30 ml/min. Only limited data are available in patients with creatinine clearance ≤ 30 ml/min and caution is advised in these patients (see section 5.2).

Elderly

No dose adjustment is required on the basis of patient age (see section 5.2).

CYP2D6 poor metabolisers

No specific dose adjustment is recommended in patients with known CYP2D6 poor metaboliser genotype, but these patients should be closely monitored for adverse events (see section 5.2).

Dose adjustment due to toxicity

Patients with poorly tolerated diarrhoea or skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose (see section 4.8). For patients unable to tolerate treatment after a therapy interruption, gefitinib should be discontinued and an alternative treatment should be considered.

Paediatric population

The safety and efficacy of **GEFIRIX** in children and adolescents aged less than 18 years have not been established. There is no relevant use of gefitinib in the paediatric population in the indication of NSCLC.

Method of administration

GEFIRIX may be taken orally with or without food, at about the same time each day. The tablet can be swallowed whole with some water or if dosing of whole tablets is not possible, tablets may be administered as a dispersion in water (non-carbonated). No other liquids should be used. Without crushing it, the tablet should be dropped in half a glass of drinking water. The glass should be swirled occasionally, until the tablet is dispersed (this may take up to 20 minutes). The dispersion should be drunk immediately after dispersion is complete (i.e. within 60 minutes). The glass should be rinsed with half a glass of water, which should also be drunk. The dispersion can also be administered through a naso-gastric or gastrostomy tube.

4.3 Contraindications

- Known hypersensitivity to gefitinib or to any of the excipients of **GEFIRIX** listed in section 6.1.
- Pregnancy and breast-feeding.

4.4 Special warnings and precautions for use

When considering the use of **GEFIRIX** as a treatment for locally advanced or metastatic NSCLC, it is important that EGFR mutation assessment of the tumour tissue is attempted for all patients. If a tumour sample is not evaluable, then circulating tumour DNA (ctDNA) obtained from a blood (plasma) sample may be used.

Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status of tumours or ctDNA should be used to avoid false negative or false positive determinations (see section 5.1).

Interstitial lung disease (ILD)

Interstitial lung disease (ILD), which may be acute in onset, has been observed in patients receiving gefitinib, and some cases have been fatal (see section 4.8). If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, **GEFIRIX** should be interrupted and the patient should be promptly investigated. If ILD is confirmed, **GEFIRIX** should be discontinued, and the patient treated appropriately.

Risk of mortality among patients who developed ILD on **GEFIRIX** or chemotherapy was higher in patients with the following risk factors: smoking, CT scan evidence of reduced normal lung (≤ 50 %), pre-existing ILD, older age (≥ 65 years old), and extensive areas adherent to pleura (≥ 50 %).

Hepatotoxicity and liver impairment

Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed, uncommonly presenting as hepatitis (see section 4.8). There have been isolated reports of hepatic failure which in some cases led to fatal outcomes. Therefore, periodic liver function testing is recommended. **GEFIRIX** should

be used cautiously in the presence of mild to moderate changes in liver function. Discontinuation should be considered if changes are severe.

Impaired liver function due to cirrhosis has been shown to lead to increased plasma concentrations of gefitinib (see section 5.2).

Interactions with other medicinal products

CYP3A4 inducers may increase metabolism of gefitinib and decrease gefitinib plasma concentrations. Therefore, concomitant administration of CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or herbal preparations containing St John's wort/Hypericum perforatum) may reduce efficacy of the treatment and should be avoided (see section 4.5).

In individual patients with CYP2D6 poor metaboliser genotype, treatment with a potent CYP3A4 inhibitor might lead to increased plasma levels of gefitinib. At initiation of treatment with a CYP3A4 inhibitor, patients should be closely monitored for **GEFIRIX** adverse reactions (see section 4.5).

International normalised ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib (see section 4.5). Patients taking warfarin and **GEFIRIX** concomitantly should be monitored regularly for changes in prothrombin time (PT) or INR.

Medicinal products that cause significant sustained elevation in gastric pH, such as proton-pump inhibitors and h_2-antagonists may reduce bioavailability and plasma concentrations of gefitinib and, therefore, may reduce efficacy. Antacids if taken regularly close in time to administration of gefitinib may have a similar effect (see sections 4.5 and 5.2).

GEFIRIX may exacerbate the neutropenic effect of vinorelbine, when used concomitantly.

Further precautions for use

Patients should be advised to seek medical advice immediately if they experience severe or persistent diarrhoea, nausea, vomiting or anorexia as these may indirectly lead to dehydration. These symptoms should be managed as clinically indicated (see section 4.8).

Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with **GEFIRIX** should be interrupted, and if symptoms do not resolve, or if symptoms recur on reintroduction of **GEFIRIX**, permanent discontinuation should be considered.

An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving **GEFIRIX** has not been established.

Gastrointestinal perforation has been reported in patients taking gefitinib. In most cases this is associated with other known risk factors, including concomitant medications such as steroids or NSAIDs, underlying history of GI ulceration, age, smoking or bowel metastases at sites of perforation.

Lactose

GEFIRIX contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **GEFIRIX**.

Sodium

GEFIRIX contains less than 1 mmol (23 mg) of sodium per dose, i.e. essentially 'sodium-free'.

4.5 Interactions with other medicines and other forms of interaction

The metabolism of gefitinib is via the cytochrome P450 isoenzyme CYP3A4 (predominantly) and via CYP2D6.

*Medicines that may increase **GEFIRIX** plasma concentrations*

Gefitinib is a substrate of p-glycoprotein (Pgp). Available data do not suggest any clinical consequences to this in vitro finding.

Medicines that inhibit CYP3A4 may decrease the clearance of gefitinib in **GEFIRIX**. Concomitant administration with potent inhibitors of CYP3A4 activity (e.g. ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin) may increase gefitinib in **GEFIRIX** plasma concentrations. The increase may be clinically relevant since adverse reactions are related to dose and exposure. The increase might be higher in individual patients with CYP2D6 poor metaboliser genotype. In situations of concomitant treatment with potent inhibitors of CYP3A4 the patient should be closely monitored for **GEFIRIX** adverse reactions.

There are no data on concomitant treatment with an inhibitor of CYP2D6 but potent inhibitors of this enzyme might cause increased plasma concentrations of gefitinib in CYP2D6 extensive metabolisers by about 2-fold (see section 5.2). If concomitant treatment with a potent CYP2D6 inhibitor is initiated, the patient should be closely monitored for adverse reactions.

*Medicines that may reduce gefitinib in **GEFIRIX** plasma concentrations*

Medicines that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations and thereby reduce the efficacy of **GEFIRIX**. Concomitant medicines that induce CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's wort, *Hypericum perforatum*), should be avoided.

Medicines that cause significant sustained elevation in gastric pH may reduce gefitinib plasma concentrations and thereby reduce the efficacy of **GEFIRIX**. High doses of short-acting antacids (example ranitidine) may have a similar effect if taken regularly close in time to administration of **GEFIRIX.**

*Medicines that may have their plasma concentrations altered by **GEFIRIX***

Gefitinib in **GEFIRIX** has limited potential to inhibit CYP2D6. When the use of CYP2D6 substrates are considered in combination with **GEFIRIX**, a dose modification of the CYP2D6 substrate should be considered especially for medicines with a narrow therapeutic window. Gefitinib inhibits the transporter protein BCRP *in vitro*, but the clinical relevance of this finding is unknown.

Other potential interactions

INR elevations and/or bleeding events have been reported in some patients concomitantly taking warfarin with gefitinib (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised not to get pregnant during therapy.

Pregnancy

There are no data from the use of gefitinib in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. **GEFIRIX** should not be used during pregnancy.

Breast-feeding

It is not known whether gefitinib is secreted in human milk. Gefitinib and metabolites of gefitinib accumulates in milk of lactating rats. **GEFIRIX** is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving **GEFIRIX** therapy (see section 4.3).

4.7 Effects on ability to drive and use machines

During treatment with gefitinib, asthenia has been reported. Therefore, patients who experience this symptom should be cautious when driving or using machines.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent reported adverse drug reactions (ADRs) are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). ADRs usually occur within the first month of therapy and are generally reversible.

Interstitial lung disease (ILD) has occurred in patients, that are often severe. Cases with fatal outcomes have been reported.

b) Tabulated summary of adverse reactions

The following side effects to be considered in patients treated with **GEFIRIX**:

System organ class	Frequent	Less frequent	Frequency unknown
Metabolism and nutrition disorders	Anorexia (mild or moderate)		

Eye disorders	Conjunctivitis, blepharitis, and dry eye* (mainly mild)	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth; Keratitis	
Vascular disorders	Haemorrhage, such as epistaxis and haematuria		
Respiratory system, thoracic and mediastinal disorders	Interstitial lung disease (often severe). Cases with fatal outcomes have been reported		
Gastrointestinal disorders	Diarrhoea (mainly mild or moderate). Vomiting (mainly mild or moderate). Nausea (mainly mild). Stomatitis (predominantly mild in nature). Dehydration (secondary to diarrhoea, nausea, vomiting or anorexia). Dry mouth* (predominantly mild).	Pancreatitis, Gastrointestinal perforation.	
Hepatobiliary disorders	Elevations in alanine aminotransferase (mainly mild to moderate). Elevations in aspartate aminotransferase (mainly mild to moderate). Elevations in total bilirubin (mainly mild to moderate).	Hepatitis**	
Skin and subcutaneous tissue disorders	Skin reactions (mainly a mild or moderate), pustular rash, sometimes itchy with dry skin, including skin fissures, on an erythematous base. Nail disorder, Alopecia, Allergic reactions, including angioedema and urticaria.	Bullous conditions including toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme. Cutaneous vasculitis.	
Renal and urinary	Asymptomatic	Haemorrhagic cystitis.	

disorders	laboratory elevations in blood creatinine. Proteinuria, Cystitis.		
General disorders and administration site conditions	Asthenia (predominantly mild), Pyrexia.		

*This adverse reaction can occur in association with other dry conditions (mainly skin reactions) seen with gefitinib.

** This includes isolated reports of hepatic failure which in some cases led to fatal outcomes.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific treatment in the event of overdose of **GEFIRIX.** However, an increase of frequency and severity of some adverse reactions is observed, mainly diarrhoea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed as clinically indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatics

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01XE02

Mechanism of action and pharmacodynamic effects

The epidermal growth factor (EGF) and its receptor (EGFR [HER1; ErbB1]) have been identified as key drivers in the process of cell growth and proliferation for normal and cancer cells. EGFR activating mutation within a cancer cell is an important factor in promotion of tumour cell growth, blocking of apoptosis, increasing the production of angiogenic factors and facilitating the processes of metastasis.

Gefitinib is a selective small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase and is an effective treatment for patients with tumours with activating mutations of the EGFR tyrosine kinase domain regardless of line of therapy. No clinically relevant activity has been shown in patients with known EGFR mutation-negative tumours.

Resistance

Most NSCLC tumours with sensitising EGFR kinase mutations eventually develop resistance to **GEFIRIX** treatment, with a median time to disease progression of 1 year. In most cases, resistance is associated with a secondary T790M mutation for which T790M targeted EGFR TKIs may be considered as a next line treatment option. Other potential mechanisms of resistance that have been reported following treatment with EGFR signal blocking agents include: bypass signalling such as HER2 and MET gene amplification and PIK3CA mutations. Phenotypic switch to small cell lung cancer has also been reported.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of gefitinib, absorption is moderately slow and peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after administration. Mean absolute bioavailability is 59 % in cancer patients. Exposure to gefitinib is not significantly altered by food (see sections 4.4 and 4.5).

Distribution

Gefitinib has a mean steady-state volume of distribution of 1400 l indicating extensive distribution into tissue. Plasma protein binding is approximately 90 %. Gefitinib binds to serum albumin and alpha 1-acid glycoprotein.

Gefitinib is a substrate for the membrane transport protein Pgp.

Biotransformation

CYP3A4 and CYP2D6 are the major P450 isozyme involved in the oxidative metabolism of gefitinib.

Gefitinib has limited potential to inhibit CYP2D6. Gefitinib shows no enzyme induction effects and no significant inhibition of any other cytochrome P450 enzyme.

Gefitinib is extensively metabolised in humans. Five metabolites have been fully identified in excreta and 8 metabolites in plasma. The major metabolite identified is O-desmethyl gefitinib, which is 14-fold less potent than gefitinib at inhibiting EGFR stimulated cell growth and has no inhibitory effect on tumour cell growth in mice. It is therefore considered unlikely that it contributes to the clinical activity of gefitinib.

The formation of O-desmethyl gefitinib has been shown, to be via CYP2D6. The role of CYP2D6 in the metabolic clearance of gefitinib has been evaluated. In poor metabolisers no measurable levels of O-desmethyl gefitinib are produced. The levels of exposure to gefitinib achieved in both the extensive and the poor metaboliser groups are wide and overlapping but the mean exposure to gefitinib is 2-fold higher in the poor metaboliser group. The higher average exposures that could be achieved by individuals with no active CYP2D6 may be clinically relevant since adverse effects are related to dose and exposure.

Elimination

Gefitinib is excreted mainly as metabolites via the faeces, with renal elimination of gefitinib and metabolites accounting for less than 4 % of the administered dose.

Gefitinib total plasma clearance is approximately 500 ml/min and the mean terminal half-life is 41 hours in cancer patients. Administration of gefitinib once daily results in 2- to 8-fold accumulation, with steady-state exposures achieved after 7 to 10 doses. At steady-state, circulating plasma concentrations are typically maintained within a 2- to 3-fold range over the 24-hour dosing interval.

Special populations

No relationships are identified between predicted steady-state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance (above 20 ml/min).

Hepatic impairment

In patients with mild, moderate or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification), there is an increase in exposure in all groups compared with healthy controls. An average 3.1-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment is observed. This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients include croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone K-30, purified water and sodium laurilsulfate.

The coating ingredient include Opadry II 85F96667, that consists of iron oxide red, iron oxide yellow, macrogol 3350, polyvinyl alcohol, talc and titanium dioxide.

6.2 Incompatabilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

GEFIRIX is packed in PVC/PVDC-Aluminum blisters packed in PET/Aluminum pouches. The pouch is further packed in an outer carton.

Pack size: 30 film-coated tablets per carton (10 tablets per blister)

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

9 DATE OF FIRST AUTHORISATION

26 October 2021

10 DATE OF REVISION OF TEXT

Not applicable

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable