Minimum Text Font Size: 7 pt in Times News Roman

SAME SIZE ARTWORK
LEAFLET SIZE: 150 mm x 420 mm
FOLDING SIZE: 150 mm x 35 mm

For the use only of a registered Medicinal Practitioner or a hospital or a Laboratory

Rx Prescription only

Gefihope 250 mg Film Coated Tablet

Gefitinib 250 mg

SPACE FOR PHARMACODE

pharmacode reading direction

COMPOSITION
Each tablet contains 250 mg of gefitinib.

PHARMACEUTICAL FORM
Film-Coated Tablets

ROUTE OF ADMINISTRATION
Oral

ACTION AND CLINICAL PHARMACOLOGY
Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors ATC code: L01EB01- GEFITINIB

Pharmacodynamics properties
Gefitinib is a selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase, commonly expressed in solid human tumours of epithelial origin. Inhibition of EGFR tyrosine kinase activity inhibits tumour growth, metastasis and angiogenesis and increases tumour cell apoptosis.

Patients that have never smoked, have adenocarcinoma histology, are female gender or are of Asian ethnicity, are more like to benefit from treatment with gefitinib. These clinical characteristics are also associated with a higher rate of EGFR mutation positive tumours.

Resistance
Most NSCLC (non-small cell lung cancer) tumours with sensitising EGFR kinase mutations eventually develop resistance to gefitinib treatment with a median time to disease progression of 1 year. In about 60% of 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 have been reported following treatment with EGFR signal blocking agents including bypass signalling such as HER2 and MET gene amplification and PIK3CA mutations. Phenotypic switch to small cell lung cancer has also been reported in 5-10% of cases.

Pharmacokinetics
Following intravenous administration, gefitinib is rapidly cleared, extensively distributed and has a mean elimination half-life of 48 hours. Following oral dosing in cancer patients, absorption is moderately slow and the mean terminal half-life is 41 hours. 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.

Absorption: Following oral administration, peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after dosing. Mean absolute bioavailability is 59% in cancer patients. Exposure to gefitinib is not significantly altered by food. Gefitinib exposure was reduced by 47% where gastric pH was maintained above pH 5

Distribution: Mean volume of distribution at steady state of gefitinib is 1400 L indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and α1-acid glycoprotein.

Metabolism: In vitro data indicate that CYP3A4 is the major P450 isozyme involved in the oxidative metabolism of gefitinib. Gefitinib has limited potential to inhibit CYP2D6.

Gefitinib shows no enzyme induction effects in animal studies and no significant inhibition (*in vitro*) of any other cytochrome P450 enzyme.

Three sites of biotransformation have been identified in the metabolism of gefitinib: metabolism of the N-propylmorpholino-group, demethylation of the methoxy- substituent on the quinazoline and oxidative defluorination of the halogenated phenyl group. Five metabolites have been fully identified in faecal extracts and the major component was O-desmethyl gefitinib, although this only accounted for 14% of the dose.

In human plasma 8 metabolites were fully identified. The major metabolite identified was O- desmethyl gefitinib, which was 14-fold less potent than gefitinib at inhibiting EGFR stimulated cell growth and had no inhibitory effect on tumour cell growth in mice. It is therefore considered unlikely that it contributes to the clinical activity of gefitinib.

The production of O-desmethyl gefitinib has been shown, in vitro, to be via CYP2D6. The role of CYP2D6 in the metabolic clearance of gefitinib has been evaluated in clinical trial in healthy volunteers genotyped for CYP2D6 status. In poor metabolisers, no measurable levels of O-desmethyl gefitinib were produced. The range of gefitinib exposures achieved in both the extensive and the poor metaboliser groups were wide and overlapping but the mean exposure to gefitinib was 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 experiences are related to dose and exposure.

Elimination: Gefitinib total plasma clearance is approximately 500 mL/min. Excretion is predominantly via the faeces with renal elimination of drug and metabolites accounting for less than 4% of the administered dose.

Special Populations: In cancer patients, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

Single dose of gefitinib 250 mg in patients with mild, moderate or severe hepatic impairment due to cirrhosis (according to Child-Pugh classification), there was 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 was observed. None of the patients had cancer, all had cirrhosis and some had hepatitis. This increase in exposure may be of clinical relevance since adverse experiences are related to dose and exposure to gefitinib.

Gefitinib has been evaluated in patients with solid tumours and normal hepatic function or, moderate or severe hepatic dysfunction due to liver metastases. Following daily dosing of 250 mg gefitinib, time to steady state, total plasma clearance and steady state exposure (C_{maxSS}, AUC_{24SS}) were similar for the groups with normal and moderately impaired hepatic function.

Data from patients with severe hepatic dysfunction due to liver metastases suggested that steady state exposures in these patients are also similar to those in patients with normal hepatic function.

INDICATIONS
Gefihope is indicated for the treatment of adult patients with locally advanced or metastatic non- small cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

DOSAGE AND ADMINISTRATION
The recommended dose of Gefihope is one 250 mg tablet once a day, taken with or without food. If a dose of Gefihope 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.

Where dosing of whole tablets is not possible, such as patients who are only able to swallow liquids, tablets may be administered as a dispersion in water. The tablet should be dropped into half a glass of drinking water (non-carbonated), without crushing, and the glass stirred until the tablet has dispersed (approximately 15 minutes) and the contents subsequently drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The liquid can also be administered via a nasogastric tube.

Gefihope is not recommended for use in children or adolescents as safety and effectiveness in these patient populations has not been studied.

No dosage adjustment is required on the basis of patient age, body weight, gender, ethnicity or renal function or in patients with moderate to severe hepatic impairment due to liver metastases.

Dosage adjustment: Patients with poorly tolerated diarrhoea or skin adverse drug reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

Breast-feeding

WARNINGS AND PRECAUTIONS
When considering the use of gefitinib as first-line treatment for locally advanced or metastatic NSCLC, it is recommended that EGFR mutation assessment of the tumour tissue is attempted for all patients. When assessing the mutation status of a patient it is important that a well-validated and robust methodology is chosen to minimise the possibility of false negative or false positive determinations. Tumour samples which are used for the diagnosis of advanced NSCLC are the preferred sample type for EGFR mutation testing. A tumour sample should be collected and tested where possible. If a tumour sample is not available or evaluable, then circulating tumour DNA (ctDNA) obtained from a blood (plasma) sample may be used. Only robust, reliable, sensitive test(s) with demonstrated utility on ctDNA should be used for the determination of EGFR mutation status of ctDNA. EGFR mutations identified in ctDNA are highly predictive of EGFR mutation positive tumours). However it is not always possible to detect EGFR mutations using this sample type (0.2% false positives, 34.3% false negatives).

In the first line setting, gefitinib should not be used in preference to doublet chemotherapy in mutation-negative patients.

Interstitial Lung Disease (ILD), which may be acute in onset, has been observed in patients receiving gefitinib, and some cases have been fatal If patients present with worsening of respiratory symptoms such as dyspnoea, cough and fever, gefitinib should be interrupted and prompt investigation initiated. If ILD is confirmed, gefitinib should be discontinued and the patient treated appropriately.

In patients with NSCLC who were receiving gefitinib or chemotherapy, the following risk factors for developing ILD (irrespective of whether the patient received gefitinib or chemotherapy) were identified:

Smoking, poor performance status (PS ≥2), CT scan evidence of reduced normal lung (≤50%), recent diagnosis of NSCLC (<6 months), pre-existing ILD, increasing age (≥55 years old) and concurrent cardiac disease. Risk of mortality among patients who developed ILD on both treatmentswas higher in patients with the following risk factors: Smoking, CT scan evidence of reduced normal lung (≤50%), pre-existing ILD, increasing age (≥65 years old), and extensive areas adherent to pleura (≥50%).

Liver function test abnormalities (including increase in alanine aminotransferase, aspartate aminotransferase, bilirubin) have been observed uncommonly presenting as hepatitis. There have been isolated reports of hepatic failure which in some cases led to fatal outcomes. Therefore, periodic liver function testing is recommended. gefitinib should be used cautiously in the presence of mild to moderate change in liver function. Discontinuation should be considered if changes are severe.

Cerebrovascular events have been reported. A relationship with gefitinib has not been established.

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations. Therefore, co-medication with CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's Wort) may reduce efficacy

International Normalised Ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin. Patients taking warfarin should be monitored regularly for changes in Prothrombin Time (PT) or INR.

Drugs that cause significant sustained elevation in gastric pH may reduce plasma concentrations of gefitinib and therefore may reduce efficacy.

Patients should be advised to seek medical advice promptly in the event of developing: Severe or persistent diarrhoea, nausea, vomiting or anorexia.

These symptoms should be managed as clinically indicated 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 gefitinib should be interrupted, and if symptoms do not resolve, or recur on reintroduction of gefitinib, permanent discontinuation should be considered.

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

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Gefitinib and vinorelbine have been used concomitantly, indicate that gefitinib may exacerbate the neutropenic effect of vinorelbine.

Gastrointestinal perforation has been reported in patients taking gefitinib. In most cases this is associated with other known risk factors, including increasing age, concomitant medications such as steroids or NSAIDS, underlying history of GI ulceration, smoking or bowel metastases at sites of perforation, Lactose intolerance This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

Sodium
Each Gefihope tablet contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

FERTILITY, PREGNANCY AND LACTATION
There are no data from the use of gefitinib in pregnant or breast-feeding women.

Studies in animals have shown reproductive toxicity. Animal studies also indicate that gefitinib and certain metabolites pass into rats breast-milk.

Women of childbearing potential must be advised to avoid becoming pregnant, and breast-feeding mothers must be recommended to discontinue nursing while receiving gefitinib therapy.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
During treatment with gefitinib, asthenia has been reported. Therefore, patients who experience this symptom should be caution when driving or using machines.

DRUG INTERACTIONS
In vitro studies have shown that the metabolism of gefitinib is predominantly via CYP3A4.

Co-administration with rifampicin (a known potent CYP3A4 inducer) in healthy volunteers reduced mean gefitinib AUC by 83% of that without rifampicin.

Co-administration with itraconazole (a CYP3A4 inhibitor) resulted in an 80 % increase in the mean AUC of gefitinib in healthy volunteers. This increase may be clinically relevant since adverse experiences are related to dose and exposure.

Co-administration of ranitidine at a dose that caused sustained elevations in gastric pH (≥ 5), resulted in a reduced mean gefitinib AUC by 47% in healthy volunteers.

INR elevations and/or bleeding events have been reported in some patients taking warfarin.

ADVERSE REACTIONS
The most commonly reported adverse drug reactions (ADRs), occurring in more than 20 % of the patients, are diarrhea, and skin reactions (including rash, acne, dry skin and pruritus). ADRs usually occur within the first month of therapy and are generally reversible. Approximately 10% of patients had a severe ADR (Common Toxicity Criteria, (CTC) grade 3 or 4). Approximately 3% of patients stopped therapy due to an ADR.

Adverse Drug Reactions (ADRs) have been assigned to the frequency categories in the table below. In assigning these frequencies no account was taken of the frequency of reports within the comparative treatment groups or whether the investigator considered it to be related to study medication.

Frequency of ADRs relating to abnormal laboratory values is based on patients with a 2 or more CTC grade change from baseline in the relevant laboratory parameters.

Table 1 Adverse drug reactions by system organ class and frequency

Metabolism and nutrition disorders	Very common	Anorexia mild or moderate (CTC grade 1 or 2).
Eye disorders	Common	Conjunctivitis, blepharitis and dry eye*, mainly mild (CTC grade 1).
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth. Keratitis (0.12%).
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria.
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease (1.3%), often severe (CTC grade 3 or 4). Cases with fatal outcomes have been reported.
Gastrointestinal disorders	Very common	Diarrhoea, mainly mild or moderate (CTC grade 1 or 2) and less commonly, severe (CTC grade 3 or 4) Vomiting, mainly mild or moderate (CTC grade 1 or 2). Nausea, mainly mild (CTC grade 1). Stomatitis, predominantly mild.(CTC grade 1)
	Common	Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia. Dry mouth*, predominantly mild (CTC grade 1).
	Uncommon	Pancreatitis. Gastrointestinal perforation.
Hepatobiliary disorders	Very common	Elevations in alanine aminotransferase, mainly mild to moderate.
	Common	Elevation in aspartate aminotransferase, mainly mild to moderate. Elevation in total bilirubin, mainly mild to moderate.
	Uncommon	Hepatitis**
Skin and subcutaneous tissue disorders	Very common	Skin reactions, mainly a mild or moderate (CTC grade 1 or 2) pustular rash, sometimes itchy with dry skin, including skin fissures, on an erythematous base.
	Common	Nail disorders. Alopecia. Allergic reactions (1.1%), including angioedema and urticaria.
	Uncommon	Palmar-plantar erythrodysaesthesia syndrome
	Rare	Bullous conditions including Toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme Cutaneous vasculitis***
Renal and urinary disorders	Common	Asymptomatic laboratory elevations in blood creatinine Proteinuria Cystitis
	Rare	Haemorrhagic cystitis***
General disorders and administration site conditions	Very common	Asthenia, predominantly mild (CTC grade 1).
	Common	Pyrexia

The frequency of adverse drug reactions relating to abnormal laboratory values are based on patients with a change from baseline of 2 or more CTC grades in the relevant laboratory parameters.

*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.

*** It was not possible to assign frequencies for cutaneous vasculitis and haemorrhagic cystitis based on the Phase III studies as there were no reports of these reactions in trials in which they could have been detected, therefore frequencies are estimated based on European Commission Guidance (September 2009), which assumes there were 3 reports across the monotherapy studies.

OVERDOSAGE
There is no specific treatment in the event of overdose of gefitinib. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed as clinically indicated.

PHARMACEUTICAL PARTICULARS
List of excipients:
Magnesium stearate, lactose monohydrate, cellulose microcrystalline,crospovidone,povidone K30, sodium laurilsulfate,purified water,sodium starch glycolate,Opadry Brown, Iron oxide red, Glycerol monocaprylocaprate, Titanium dioxide,iron oxide yellow,iron oxide black.

INCOMPATIBILITIES
Not applicable

SHELF LIFE
48 months

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C.

NATURE AND CONTENTS OF CONTAINER
Transparent PVC/ aluminium blisters or PVC/ PCTFE (Aclar)/ Aluminium blisters. Pack size of 30 film-coated tablets.

SPECIAL PRECAUTIONS FOR DISPOSAL
None

DATE OF REVISION: 15.09.2023

Manufactured at:
Genepharm S.A
18® km, Marathonos Avenue,
Pallini Attiki, 15351, Greece.

Product Registration Holder:
glenmark
Glenmark Pharmaceuticals (Malaysia) Sdn Bhd
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No. 2, Jalan Kerinchi,
59200 Kuala Lumpur, Malaysia

PE00000 **MY**

420 mm

150 mm

ICONGRAPHICS CODE:

PANTONE SHADE

PANTONE BLACK PROCESS C

Supersedes Artwork Code:

PHARMACODE :