Hovid Gefitinib Tablets 250 mg

VIGEF01-var (SIN)

DESCRIPTION
Hovid Gefitinib tablets 250 mg are round, biconvex face, brown film-coated, debossed with "QL" on one side and plain on the other side.

COMPOSITION
Each film coated tablet consists of gefitinib 250 mg.
Excipients: Lactose monohydrate, microcystalline cellulose PH101, povidone, croscarmellose sodium, sodium lauryl sulfate, purified water, magnesium stearate, Opadry 85F665001 Brown (polyvinyl alcohol-part hydrolysed, macrogol, talc, titanium dioxide, iron oxide red, ferrosoferric oxide, iron oxide yellow).

PHARMACODYNAMICS
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.

Clinical characteristics of never smoker, adenocarcinoma histology and female gender have been shown to be independent predictors of positive EGFR mutation status. Asian patients also have a higher incidence of EGFR mutation-positive tumours.

Resistance
Most NSCLC tumours with sensitizing 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 of gefitinib, 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. In a trial in healthy volunteers where gastric pH was maintained above pH 5, gefitinib exposure was reduced by 47%.

Distribution:
Mean volume of distribution at steady state of gefitinib is 1400L indicating extensive distribution into tissue. Plasma protein binding is approximately 90%. Gefitinib binds to serum albumin and alpha1-acid glycoprotein.

Metabolism:
In vitro data indicate that CYP3A4 and CYP2D6 are the major P450 isozymes involved in the oxidative metabolism of gefitinib.

In vitro studies have shown that gefitinib has limited potential to inhibit CYP2D6. In a clinical trial in patients, gefitinib was co-administered with metoprolol (a CYP2D6 substrate). This resulted in a small (35%) increase in exposure to metoprolol, which is not considered to be clinically relevant.

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 a 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 population based data analyses in cancer patients, no relationships were identified between predicted steady state trough concentration and patient age, body weight, gender, ethnicity or creatinine clearance.

In a phase I open-label study of single dose 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 a clinical trial conducted in 41 patients with solid tumours and normal hepatic function, or moderate or severe hepatic dysfunction due to liver metastases. It was shown that following daily dosing of 250 mg gefitinib, time to steady state, total plasma clearance and steady state exposure ($C_{max,ss}$, $AUC_{0-24,ss}$) were similar for the groups with normal and moderately impaired hepatic function. Data from 4 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
Hovid Gefitinib 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 EGFR-TK.

CONTRAINDICATIONS
Known severe hypersensitivity to the active substance or to any of the excipients of this product.

WARNING AND PRECAUTIONS
When considering the use of gefitinib as first-line treatment for 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. 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 a Japanese Pharmacoepidemiological case control study in 3159 patients with NSCLC who were followed up for 12weeks when 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 treatments was 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 increases 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 changes in liver function. Discontinuation should be considered if changes are severe.

Cerebrovascular events have been reported in clinical studies of gefitinib. 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.

Gefitinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Recent corneal surgery and contact lens wearing are known to be independent risk factors for ocular toxicity including corneal erosion.

In a phase I/II trial of gefitinib and radiation in paediatric patients, newly diagnosed with brain stem glioma or incompletely resected supratentorial malignant glioma, 4 cases (1 fatal) of CNS haemorrhages were reported from 45 patients enrolled. A further case of CNS haemorrhage has been reported in a child with an ependymoma from a trial with gefitinib alone. An increased risk of cerebral haemorrhage in adult patients with NSCLC receiving gefitinib has not been established.

Phase II clinical trial data, where 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.

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 rat's 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.

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. Although interaction studies with other CYP3A4 inhibitors have

not been performed it is expected that drugs such as ketoconazole, clotrimazole, ritonovir would also inhibit gefitinib metabolism.
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.

MAIN SIDE/ ADVERSE EFFECTS

Summary of the safety profile
The most frequently reported adverse drug reactions, occurring in more than 20% of the patients, 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.

Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class		Adverse drug reactions
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 3-4). Cases with fatal outcomes have been reported
Gastrointestinal disorders	Very Common	Diarrhoea, mainly mild or moderate (CTC grade 1 or 2)
		Vomiting, mainly mild or moderate (CTC grade 1 or 2)
		Nausea, mainly mild (CTC grade 1)
		Stomatitis, predominantly mild in nature (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	Elevations in aspartate aminotransferase, mainly mild to moderate
		Elevations 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 disorder
		Alopecia
		Allergic reactions (1.1%), including angioedema and urticaria
	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 is 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.

From a phase III double blind clinical trial (1692 patients) comparing gefitinib plus best supportive care (BSC) to placebo plus BSC in patients with advanced NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory or intolerant to their most recent regimen, the incidence of ILD-type events in the overall population was similar, and approximately 1% in both treatment arms. The majority of ILD-type events reported were from patients of Oriental ethnicity and the ILD incidence among patients of Oriental ethnicity receiving gefitinib therapy and placebo was similar, approximately 3% and 4% respectively. One ILD-type event was fatal, and this occurred in a patient receiving placebo.

In a Post-Marketing Surveillance study in Japan (3350 patients), the reported rate of ILD-type events in patients receiving gefitinib was 5.8%.

In a Japanese Pharmacoepidemiological case control study in patients with NSCLC, the crude cumulative incidence of ILD (unadjusted for imbalances in patient characteristics) at 12 weeks follow-up was 4.0% in patients receiving gefitinib and 2.1% in those receiving chemotherapy and the adjusted odds ratio (OR) of developing ILD was 3.2 (95% confidence interval [CI] 1.9 to 5.4) for gefitinib versus chemotherapy. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4 weeks of treatment (adjusted OR 3,8; 95% CI 1,9 to 7,7); thereafter the relative risk was lower (adjusted OR 2,5; 95% CI 1,1 to 5,8).

In a phase III open-label clinical trial (1217 patients) comparing gefitinib to carboplatin/paclitaxel doublet chemotherapy as first-line treatment in selected patients with advanced NSCLC in Asia, the incidence of ILD-type events was 2.6% on the gefitinib treatment arm versus 1.4% on the carboplatin/paclitaxel treatment arm.

OVERDOSE AND TREATMENT

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. In phase I clinical trials, a limited number of patients were treated with daily doses of up to 1000 mg. An increase of frequency and severity of some adverse reactions was observed, mainly diarrhoea and skin rash.

DOSAGE AND ADMINISTRATION

Treatment with Hovid Gefitinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

Dosage
The recommended dosage of Hovid Gefitinib 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.

Hepatic impairment
No dosage adjustment is required in patients with moderate to severe hepatic impairment due to liver metastases.

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 aspartate transaminase (AST), alkaline phosphatase or bilirubin due to liver metastases.

Renal impairment
No dosage adjustment is required in patients with mild to moderate renal impairment.

Elderly
No dose adjustment is required on the basis of patient age.

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.

Dose adjustment due to toxicity.
Patients with poorly tolerated diarrhea or skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement if the 250 mg dose.

In the event of acute onset or worsening of pulmonary symptoms (dyspnoea, cough, fever) gefitinib therapy should be interrupted and a prompt investigation of these symptoms should occur and appropriate treatment initiated. If interstitial lung disease is confirmed, gefitinib should be discontinued and the patient treated appropriately.

Patients who develop onset of new eye symptoms such as pain should be medically evaluated and managed appropriately, including gefitinib therapy interruption and removal of an aberrant eyelash if present. After symptoms and eye changes have resolved, the decision should be made concerning reinstatement of the 250 mg daily dose.

Method of administration
The tablet 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.

Storage: Store below 30°C. Store in the original container.

Presentation/ Packing: 30 film-coated tablets in PVC Aluminium or PCTFE/PVC Aluminium blisters.

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