Hovid Gefitinib Tablets 250 mg

VIGEFxx-0

DESCRIPTION
Round, biconvex face, brown film-coated, debossed with "QL" on one side and plain on the other side.

COMPOSITION
Each film-coated tablet contains: Gefitinib 250 mg.

PHARMACODYNAMICS
Hovid Gefitinib belongs to drug class antineoplastic agents or protein kinase inhibitors.

The epidermal growth factor (EGF) and its receptor (EGFR [HER1; ErbB1]) have been identified as key drive 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.

Most NSCLC tumours with sensitising EGFR kinase mutations eventually develop resistance to gefitinib treatment, with a median time to disease progression of 1 year.

PHARMACOKINETICS
Absorption and Distribution
Following oral administration of gefitinib, absorption is moderately slow and peak plasma concentrations of gefitinib typically occur at 3 to 7 hours after administration. Exposure to gefitinib is not significantly altered by food.

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.

Biotransformation
Gefitinib is extensively metabolised in humans. Five metabolites have been fully identified in excreta and 8 metabolites in plasma where the major metabolite identified was O-desmethyl gefitinib.

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.

Hepatic impairment
3-fold increase in exposure to gefitinib in patients with moderate and severe hepatic impairment was observed.

INDICATIONS
Hovid Gefitinib 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.

CONTRAINDICATIONS
Hovid Gefitinib is contraindicated in those that are:
- Hypersensitive to the active substance or to any of the excipients in Hovid Gefitinib
- Breast-feeding

WARNING AND PRECAUTIONS
When considering the use of Hovid Gefitinib 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.

Interstitial lung disease (ILD)
Interstitial lung disease (ILD), which may be acute in onset, has been observed in 1.3% of patients receiving gefitinib, and some cases have been fatal. If patients experience worsening of respiratory symptoms such as dyspnoea, cough and fever, Hovid Gefitinib should be interrupted and the patient should be promptly investigated. If ILD is confirmed, Hovid Gefitinib should be discontinued and the patient treated appropriately.

Hepatotoxicity and liver impairment
Liver function test abnormalities (including increases in alanine aminotransferase, aspartate aminotransferase, and 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. Impaired liver function due to cirrhosis has been shown to lead to increased plasma concentrations of gefitinib.

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.

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 gefitinib adverse reactions.

International normalised ratio (INR) elevations and/or bleeding events have been reported in some patients taking warfarin together with gefitinib. Patients taking warfarin and gefitinib 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.

Lactose
Hovid Gefitinib contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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.

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 if symptoms recur on reintroduction of gefitinib, permanent discontinuation should be considered.

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.

PREGNANCY AND LACTATION
Pregnancy
Hovid Gefitinib should not be used during pregnancy unless clearly necessary.

Lactation
Gefitinib is contraindicated during breast-feeding and therefore breast-feeding must be discontinued while receiving gefitinib therapy.

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

Active substances that may increase gefitinib plasma concentrations
- Substances that inhibit CYP3A4 may decrease the clearance of gefitinib. Concomitant administration with potent inhibitors of CYP3A4 activity (e.g. ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin, telithromycin) may increase gefitinib 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 gefitinib adverse reactions.
- Concomitant treatment with an inhibitor of CYP2D6 enzyme might cause increased plasma concentrations of gefitinib in CYP2D6 extensive metabolisers. If concomitant treatment with a potent CYP2D6 inhibitor is initiated, the patient should be closely monitored for adverse reactions.

Active substances that may reduce gefitinib plasma concentrations
- Substances that are inducers of CYP3A4 activity may increase metabolism and decrease gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. Concomitant medicinal products that induce CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, barbiturates or St John's wort, *Hypericum perforatum*), should be avoided.
- Substances that cause significant sustained elevation in gastric pH may reduce gefitinib plasma concentrations and thereby reduce the efficacy of gefitinib. High doses of short-acting antacids may have a similar effect if taken regularly close in time to administration of gefitinib.

Active substances that may have their plasma concentrations altered by gefitinib
When the use of CYP2D6 substrates are considered in combination with gefitinib, a dose modification of the CYP2D6 substrate should be considered especially for products with a narrow therapeutic window.

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

MAIN SIDE/ ADVERSE EFFECTS
Summary of the safety profile
The most frequently reported adverse drug reactions 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.

System organ class		Adverse drug reactions
Metabolism and nutrition disorders	Very Common	Anorexia mild or moderate
Eye disorders	Common	Conjunctivitis, blepharitis, and dry eye*, mainly mild
	Uncommon	Corneal erosion, reversible and sometimes in association with aberrant eyelash growth
		Keratitis
Vascular disorders	Common	Haemorrhage, such as epistaxis and haematuria
Respiratory, thoracic and mediastinal disorders	Common	Interstitial lung disease, often severe. Cases with fatal outcomes have been reported
Gastrointestinal disorders	Very Common	Diarrhoea, mainly mild or moderate
		Vomiting, mainly mild or moderate
		Nausea, mainly mild
		Stomatitis, predominantly mild in nature
	Common	Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia
		Dry mouth*, predominantly mild
	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 pustular rash, sometimes itchy with dry skin, including skin fissures, on an erythematous base
	Common	Nail disorder
		Alopecia
		Allergic reactions, 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
	Common	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.

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.

OVERDOSE AND TREATMENT
There is no specific treatment in the event of overdose of gefitinib.

An increase of frequency and severity of some adverse reactions was 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.

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.

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

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

Renal impairment
No dose adjustment is required in patients with impaired renal function at creatinine clearance >20 ml/min.

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 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. For patients unable to tolerate treatment after a therapy interruption, gefitinib should be discontinued and an alternative treatment should be considered.

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.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

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

Presentation/ Packing: Blisters of 3x10's

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