

P18-0774R100/150/90
004020
Erlotinib 100mg and 150mg
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ERLOTINIB Intega
Erlotinib 100mg and 150mg Film-Coated Tablets
Antineoplastic agent, ATC code L01EB02

PHARMACEUTICAL FORM

ERLOTINIB Intega Film Coated Tablet 100mg, 150mg
ERLOTINIB Intega Film Coated Tablet 100mg: White to yellowish, round biconvex, film-coated tablet, engraved with "100" on one side.
ERLOTINIB Intega Film Coated Tablet 150mg: White to yellowish, round biconvex, film-coated tablet, engraved with "150" on one side.
Qualitative and Quantitative Composition
Active ingredient: erlotinib.

One film-coated tablet of each strength contains erlotinib hydrochloride, corresponding to 100mg and 150mg of erlotinib.

For excipients, see section on List of Excipients

CLINICAL PARTICULARS

Therapeutic Indications

Non-small cell lung cancer

ERLOTINIB Intega is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR activating mutations. ERLOTINIB Intega is indicated for maintenance treatment in patients with locally advanced or metastatic NSCLC with EGFR activating mutations who have not progressed after first-line chemotherapy. ERLOTINIB Intega is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Pancreatic Cancer

ERLOTINIB Intega in combination with gemcitabine is indicated for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Dosage and Method of Administration

Standard Dosage

Non-small cell lung cancer

EGFR mutation testing should be performed prior to initiation of ERLOTINIB Intega as first-line or maintenance therapy in patients with locally advanced or metastatic NSCLC.

The recommended daily dose of ERLOTINIB Intega is 150 mg taken at least one hour before or two hours after the ingestion of food.

Pancreatic Cancer

The recommended daily dose of ERLOTINIB Intega is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the package insert of gemcitabine for the pancreatic cancer indication).

Special Dosage Instructions

Drug Interactions: Concomitant use of CYP 3A4 substrates and modulators may require dose adjustment (see section on Interactions with other Medicinal Products and other forms of interaction).

When dose adjustment is necessary, it is recommended to reduce in 50 mg steps (see sections on Warnings and Precautions and Interactions with other Medicinal Products and other forms of interaction).

Hepatic impairment: Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function, caution should be used when administering ERLOTINIB Intega to patients with hepatic impairment. Dose reduction or interruption of ERLOTINIB Intega should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic impairment (see sections on Warnings & Precautions (Hepatic, hepatic failure) and Pharmacokinetics in Special Populations).

Renal impairment: The safety and efficacy of ERLOTINIB Intega has not been studied in patients with renal impairment. (see section Pharmacokinetics in Special Populations).

Pediatric use: The safety and efficacy of ERLOTINIB Intega in the approved indications has not been established in patients under the age of 18 years.

Smokers: Cigarette smoking has been shown to reduce erlotinib exposure by 50-60%. The maximum tolerated dose of ERLOTINIB Intega in NSCLC patients who currently smoke cigarettes was 300 mg. The 300mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150mg dose in patients who continue to smoke cigarettes (see section on Interactions with other Medicinal Products and other forms of interaction and section on Pharmacokinetics in Special Populations).

Contraindications

ERLOTINIB Intega is contraindicated in patients with severe hypersensitivity to erlotinib or to any component of ERLOTINIB Intega.

Special Warnings and Special Precautions for Use

Assessment of EGFR mutation status: When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Interstitial Lung Disease: Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib for treatment of NSCLC (non-small cell lung carcinoma), pancreatic cancer or other advanced solid tumors.

Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung drug disease, idiopathic bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. These ILD-like events started from a few days to several months after initiating erlotinib therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment initiated as necessary (see section on Undesirable Effects).

Diarrhea: Diarrhea has occurred in patients on erlotinib and moderate or severe diarrhea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration. (See section on Undesirable Effects).

There have been rare reports of hypokalaemia and renal failure (including fatalities). Some cases were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia, while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatic failure: Rare cases of hepatic failure (including fatalities) have been reported during use of erlotinib. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered. Erlotinib dosing should be interrupted if changes in liver function are severe (see section on Undesirable Effects).

Gastrointestinal perforation: Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation (see section on Undesirable Effects).

Bullosis and exfoliative skin disorders: Bullosis, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal (see section on Undesirable Effects). Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullosis, blistering or exfoliating conditions.

Ocular Disorders: Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment which are also risk factors for corneal perforation/ulceration.

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 eye should be referred promptly to an ophthalmology specialist.

If a diagnosis of ulcerative keratitis is confirmed, treatment with erlotinib should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. Erlotinib should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.

Drug interactions: Erlotinib has a potential for clinically significant drug-drug interactions. (See section on Interactions with other Medicinal Products and other forms of interaction).

Interactions with other Medicinal Products and other Forms of Interaction

Erlotinib is a potent inhibitor of CYP1A1, and a moderate inhibitor of CYP3A4 and CYP2C8, as well as a strong inhibitor of glucuronidation by UGT1A1 in vitro. The physiological relevance of the strong inhibition of CYP1A1 is unknown due to the very limited expression of CYP1A1 in human tissues.

The inhibition of glucuronidation may cause interactions with medicinal products which are substrates of UGT1A1 and exclusively cleared by this pathway. Patients with low expression levels of UGT1A1 or genetic glucuronidation disorders (e.g., Gilbert's disease) may exhibit increased serum concentrations of bilirubin and must be treated with caution.

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 CYP1B1 in tumour tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances which are metabolised by, or are inhibitors or inducers of, these enzymes. Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Concomitant use of erlotinib with ketoconazole (200 mg orally twice daily for 5 days), a potent CYP3A4 inhibitor, resulted in an increase of erlotinib exposure and increase in C_{max} when compared to erlotinib alone. Therefore, caution should be used when erlotinib is combined with a potent CYP3A4 inhibitor, e.g., azole antifungals (i.e., ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin or combined CYP3A4/CYP1A2 inhibitors. When erlotinib was co-administered with clarithromycin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure (AUC) and maximum concentration (C_{max}) also increased. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g., fluvoxamine) are combined with erlotinib. In these situations, the dose of erlotinib should be reduced if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with erlotinib and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety (see section on Special Warnings and Special Precautions (including renal and liver function and serum electrolytes)) is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting. Reduced exposure may also occur under other inducers e.g., phenytoin, carbamazepine, barbiturates or St. John's Wort (*Hypericum perforatum*). Caution should be observed when these active substances are combined with erlotinib.

Pre-treatment or co-administration of erlotinib did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease, which was however not attributed to effects on CYP3A4 activity. Erlotinib has not shown to affect pharmacokinetics of the concomitantly administered CYP3A4/C28 substrate paclitaxel. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely.

Interaction with coumarin-derived anticoagulants, including warfarin, leading to increased International Normalized Ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving erlotinib. Patients taking coumarin-derived anticoagulants should be monitored regularly for any changes in prothrombin time or INR.

The combination of erlotinib and a statin may increase the potential for statin-induced myopathy, including rhabdomyolysis, which was observed rarely.

Patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with erlotinib, as plasma erlotinib concentrations are reduced otherwise. The clinical effect of the decreased exposure has not been formally assessed but it is likely to be clinically significant. Erlotinib is a substrate for the P-glycoprotein active substance transporter. Concomitant administration of inhibitors of P-gp, e.g., cyclosporine and verapamil, may lead to altered distribution and/or altered elimination of erlotinib. The consequences of this interaction for e.g., CNS toxicity has not been established. Caution should be exercised in such situations.

Erlotinib is characterised by a decrease in solubility at pH above 5. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure (AUC) and C_{max}. There was no change to T_{max} or t_{1/2}. Therefore, concomitant administration of drugs reducing gastric acid production with erlotinib should be avoided where possible. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. If patients need to be treated with such drugs, then an H₂-receptor antagonist such as ranitidine should be considered and used in a staggered manner. Erlotinib must be taken at least 2 hours before or 10 hours after the H₂-receptor antagonist dosing. Smokers should be advised to stop smoking as cigarette smoking, which is known to induce CYP1A1 and CYP1A2, has been shown to reduce erlotinib exposure.

There were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Erlotinib increases platinum concentrations, however, the magnitude of this difference is not considered to be clinically relevant. In clinical practice, there may be other co-factors leading to an increased exposure to carboplatin like renal impairment. There were no significant effects of carboplatin or paclitaxel on the pharmacokinetics of erlotinib.

Capecitabine may increase erlotinib concentrations. There were no significant effects of erlotinib on the pharmacokinetics of capecitabine.

Use in Special Populations

Females and Males of Reproductive Potential

Contraception, female

Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy.

Pregnancy

There are no adequate or well controlled studies in pregnant women using erlotinib. Studies in animals have shown some reproductive toxicity (see sections on Impairment of Fertility and Reproductive toxicity). The potential risk for humans is unknown. Women of childbearing potential must be advised to avoid pregnancy while on erlotinib. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus.

Lactation

Nursing mothers: It is not known whether erlotinib is excreted in human milk. No studies have been conducted to assess the impact of erlotinib on milk production or its presence in breast milk. As the potential for harm to the nursing infant is unknown, mothers should be advised against breastfeeding while receiving erlotinib and for at least 2 weeks after the final dose.

Pediatric Use

The safety and efficacy of erlotinib in the approved indications has not been established in patients under the age of 18 years (see sections on Special Dosage Instructions and Pharmacokinetics in Special Populations).

Geriatric Use

See section Pharmacokinetics in Special Populations.

Renal Impairment

See sections Special Dosage Instructions and, Pharmacokinetics in Special Populations.

Hepatic Impairment

Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases (see section on Special Warnings and Special Precautions). Safety and efficacy have not been studied in patients with severe hepatic impairment. (see section on Special Dosage Instructions)

Effects on Ability to Drive and Use Machines
Erlotinib has no or negligible influence on the ability to drive and use machines.

Undesirable Effects
The incidence of adverse drug reactions (ADRs) reported with erlotinib alone or in combination with chemotherapy are summarized in the tables below.

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000).

Table 1 ADRs occurring in patients in BR.21 (treated with erlotinib) and PA.3 (treated with erlotinib plus gemcitabine) studies and ADRs occurring more than placebo in BR.21 (treated with erlotinib) and PA.3(treated with erlotinib plus gemcitabine) studies

NCI-CTC Grade	Frequency category of highest incidence
MedDRA Preferred Term	
Infections and infestations	
Infection*	very common
Metabolism and nutrition disorders	
Anorexia	very common
Weight decreased	very common
Eye disorders	
Conjunctivitis	very common
Keratoconjunctivitis sicca	very common
Psychiatric disorders	
Depression	very common
Nervous system disorders	
Headache	very common
Neuropathy	very common
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	very common
Cough	very common
Gastrointestinal disorders	
Diarrhea	very common
Nausea	very common
Vomiting	very common
Stomatitis	very common
Abdominal pain	very common
Dyspepsia	very common
Flatulence	very common
Skin and subcutaneous tissue disorders	
Rash	very common
Pruritus	very common
Dry skin	very common
Alopecia	very common
General disorders and administration site condition	
Fatigue	very common
Pyrexia	very common
Rigors	very common

* Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis

Further information on ADRs of special interest

The following ADRs have been observed in patients who received erlotinib 150 mg as monotherapy or 100 mg or 150 mg in combination with gemcitabine.

Very common ADRs are presented in Table 1, ADRs in other frequency categories are summarized below.

Gastrointestinal Disorders

Gastrointestinal perforations have been reported uncommonly (in less than 1% of patients) with erlotinib treatment, in some cases with a fatal outcome (see section on Warnings and Precautions).

Cases of gastrointestinal bleeding have been reported commonly (including some fatalities), some associated with concomitant warfarin administration (See also Section Interactions with other Medical Products and other Forms of Interaction), and some with concomitant NSAIDs.

Laboratory Disorders

Liver function test abnormalities (including raised ALT, AST, bilirubin) have been observed commonly in clinical trials of erlotinib. In study PA3, these occurred very commonly. They were mainly mild or moderate in severity, transient in nature or associated with liver metastases.

Rare cases of hepatic failure (including fatalities) have been reported during use of erlotinib. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications.

Eye Disorders

Corneal abrasions or perforations have been reported very rarely in patients receiving erlotinib treatment (see section on Warnings and Precautions). Keratitis and conjunctivitis has been reported commonly with erlotinib.

Abnormal eyelash growth including, in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported (see section on Warnings and Precautions).

Respiratory, thoracic and mediastinal disorders

There have been uncommon reports of serious interstitial lung disease (ILD-like events, including fatalities), in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. (See section on Special Warnings and Special Precautions for Use). Cases of epistaxis have also been reported commonly in both the NSCLC and the pancreatic cancer trials.

Skin and subcutaneous tissue disorders

Rash has been reported very commonly in patients receiving erlotinib and, in general, manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. Acne, dermatitis acneiform and folliculitis have been observed commonly, most of these events were mild or moderate and non-serious. For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g., mineral containing) may be advisable. Skin fissures, mostly non-serious, were reported commonly and in the majority of cases were associated with rash and dry skin. Other mild skin reactions such as hyperpigmentation have been observed uncommonly (in less than 1% of patients). Blisters, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal (see section on Warnings and Precautions).

Hair and nail changes, mostly non-serious, were reported in clinical trials, e.g., paronychia was reported commonly and hirsutism, eyelash eyebrow changes and brittle and loose nails were reported uncommonly.

Overdose

Single oral doses of erlotinib up to 1000 mg in healthy subjects and up to 1600 mg in cancer patients have been tolerated. Repeated twice daily doses of 200 mg in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, severe adverse events such as diarrhea, rash, and possibly liver transaminase elevation may occur above the recommended dose of 150 mg. In case of suspected overdose erlotinib should be withheld and symptomatic treatment administered.

PHARMACOLOGICAL PROPERTIES AND EFFECTS

Pharmacodynamic Properties

Mechanism of Action

Erlotinib potently inhibits the intracellular phosphorylation of HER1/EGFR receptor. HER1/EGFR receptor 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.

Pharmacokinetic Properties

Absorption

Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 4 hours after oral dosing. Erlotinib has an estimate of bioavailability of 59%. The exposure after an oral dose may be increased by food.

Following absorption, erlotinib is highly bound in blood, with approximately 95% bound to blood components, primarily to plasma proteins (i.e., albumin and alpha-1 acid glycoprotein [AAG]), with a free fraction of approximately 5%.

Distribution

Erlotinib has a mean apparent volume of distribution of 232l and distributes into tumor tissue of humans.

Metabolism

Erlotinib is metabolised in humans by hepatic cytochrome P450 enzymes, primarily by CYP3A4 and to a lesser extent by CYP1A2. Extrahepatic metabolism by CYP3A4 in intestine, CYP1A1 in lung, and CYP1B1 in tumour tissue potentially contribute to the metabolic clearance of erlotinib. In vitro studies indicate approximately 80-95% of erlotinib metabolism is by the CYP3A4 enzyme. 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 of erlotinib produced by O-demethylation of either side chain have comparable potency to erlotinib in nonclinical in vitro assays and in vivo tumor models. They are present in plasma at levels that are <10% of erlotinib and display similar pharmacokinetics as erlotinib. The metabolites and trace amounts of erlotinib are excreted predominantly via the feces (>90%), with renal elimination accounting for only a small amount of an oral dose.

Elimination

Clearance

Single agent erlotinib show 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. No significant relationships between predicted apparent clearance and patient age, body weight, gender, and ethnicity were observed.

Patient factors, which correlate with erlotinib pharmacokinetics, are serum total bilirubin, AAG concentrations and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a slower rate of erlotinib clearance. Smokers had a higher rate of erlotinib clearance.

Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

Exposure

Following a 150 mg oral dose of erlotinib, at steady state, the median time to reach maximum plasma concentrations is approximately 4.0 hours with median maximum plasma concentrations achieved of 1,995 ng/ml. Prior to the next dose at 24 hours, the median minimum plasma concentrations are 1,238 ng/ml. Median AUC achieved during the dosing interval at steady state are 41,300 mcg*hr/ml.

Pharmacokinetics in special populations

Hepatic impairment: Erlotinib is mainly cleared by the liver. Erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh score 7-9) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases.

Renal impairment: Erlotinib and its metabolites are not significantly excreted by the kidneys, as less than 9% of a single dose is excreted in the urine.

Smokers: Cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib. Current smokers should be advised to stop smoking while taking erlotinib, as plasma concentrations could be reduced otherwise.

Nonclinical safety

Not applicable

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet core

Lactose monohydrate
Cellulose, microcrystalline
Sodium starch glycolate
Magnesium stearate
Poly(vinyl alcohol) (E1203)
Titanium Dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)
Methacrylic Acid - Ethyl Acrylate Copolymer (1:1), type A
Sodium Hydrogen Carbonate

Storage and Stability

Store below 30°C. ERLOTINIB Intega should not be used after the expiry date (EXP) shown on the pack.

PACKS

100 mg tablets 30
150 mg tablets 30

Product Registration Holder

Intega Sdn Bhd
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