Date of approval: 23 August 2022

Approved Professional Information for BINIT 25, 100 and 150

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BINIT 25 film-coated tablets

BINIT 100 film-coated tablets

BINIT 150 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BINIT 25: Each film-coated tablet contains 25 mg erlotinib (as hydrochloride).

BINIT 100: Each film-coated tablet contains 100 mg erlotinib (as hydrochloride).

BINIT 150: Each film-coated tablet contains 150 mg erlotinib (as hydrochloride).

Excipients with known effect:

Contains sugar.

BINIT 25: Each film-coated tablet contains 13,2 mg lactose monohydrate.

BINIT 100: Each film-coated tablet contains 52,7 mg lactose monohydrate.

BINIT 150: Each film-coated tablet contains 79,0 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

BINIT 25: White to off-white, round, film-coated tablets, debossed with ‘913’ on one side and plain

on the other side.

BINIT 100: White to off-white, round, film-coated tablets, debossed with ‘914’ on one side and plain on the other side.

BINIT 150: White to off-white, round, film-coated tablets, debossed with ‘915’ on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC)

BINIT is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) activating mutation after failure of at least one prior chemotherapy regimen.

BINIT was not effective after platinum-based therapy that included gemcitabine.

BINIT monotherapy is indicated for the maintenance treatment of patients having received first line platinum-based (other than gemcitabine + cisplatin) doublets chemotherapy for locally advanced or metastatic NSCLC. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours (see section 5.1).

Bronchial adenocarcinoma

BINIT is indicated for the first-line treatment of patients with locally advanced or metastatic (stage 4) bronchial adenocarcinoma whose tumours have demonstrated EGFR activating mutations and who have never smoked and had Eastern cooperative oncology group (ECOG) performance status of 0 – 1. When prescribing BINIT, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR-negative tumours (see section 5.1).

Pancreatic cancer

BINIT in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

4.2 Posology and method of administration

Posology

BINIT treatment should be supervised by a medical practitioner experienced in the use of anticancer therapies.

Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section 4.5). Where dose adjustment is necessary, reduce in 50 mg steps.

Non-small cell lung cancer and bronchial adenocarcinoma

EGFR mutation testing should be performed prior to initiation of BINIT therapy in chemo-naïve patients with advanced or metastatic NSCLC and bronchial adenocarcinoma. The recommended dose is 150 mg daily taken at least 1 hour before or two hours after the ingestion of food. Where dose adjustment is necessary, reduce in 50 mg steps.

Pancreatic cancer

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

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 BINIT to patients with hepatic impairment (see section 5.2). BINIT should not be used in patients with severe hepatic dysfunction (AST/SGOT and ALT/SGPT > 5 x ULN). Dose reduction or interruption of BINIT should be considered if severe adverse reactions occur. Safety and efficacy have not been studied in patients with severe hepatic dysfunction.

Renal impairment

The safety and efficacy of BINIT has not been studied in patients with renal impairment (see section 5.2). BINIT should not be used in patients with severe renal impairment.

Paediatric use

The safety and efficacy of BINIT have 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 BINIT in NSCLC and bronchial adenocarcinoma patients who currently smoke cigarettes was 300 mg. The 300 mg dose did not show improved efficacy in second line treatment after failure of chemotherapy compared to the recommended 150 mg dose in patients who continue to smoke cigarettes.

Method of administration

Oral.

4.3 Contraindications

Severe hypersensitivity to erlotinib or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of BINIT as a first line or maintenance treatment for locally advanced or metastatic NSCLC, it is important that the EGFR mutation status of a patient is determined. A validated, robust, reliable and sensitive test with a prespecified positivity threshold and demonstrated utility for the determination of EGFR mutation status, using either tumour DNA derived from a tissue sample or circulating free DNA (cfDNA) obtained from a blood (plasma) sample, should be performed according to local medical practice. If a plasma-based cfDNA test is used and the result is negative for activating mutations, perform a tissue test wherever possible due to the potential for false negative results from a plasma-based test.

Smokers

Current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. The degree of reduction is likely to be clinically significant (see sections 4.2, 4.5 and 5.2).

Interstitial lung disease (ILD)

Cases of ILD-like events, including fatalities, have been reported less frequently in patients receiving BINIT for treatment of NSCLC, pancreatic cancer or other advanced solid tumours. A pivotal study BR.21 in NSCLC revealed that the incidence of ILD (0,8 %) was the same in both the placebo and erlotinib groups. In a meta-analysis of NSCLC randomised controlled clinical trials, the incidence of ILD-like events was 0,9 % in erlotinib compared to 0,4 % in patients in the control arms. In a pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2,5 % in the erlotinib plus gemcitabine group versus 0,4 % in the placebo plus gemcitabine treated group. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia,

interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), alveolitis, and lung infiltration. Symptoms started from a few days to several months after initiating erlotinib therapy. Confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections were frequent.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, BINIT therapy should be interrupted pending diagnostic evaluation. Patients treated concurrently with BINIT and gemcitabine should be monitored carefully for the possibility to develop ILD-like toxicity. If ILD is diagnosed, BINIT should be discontinued and appropriate treatment initiated as necessary (see section 4.8).

Diarrhoea, dehydration, electrolyte imbalance and renal failure

Diarrhoea (including very rare cases with a fatal outcome) has occurred in approximately 50 % of patients on erlotinib and moderate or severe diarrhoea should be treated with e.g. loperamide. In some cases dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, BINIT therapy should be interrupted and appropriate measures should be taken to treat the dehydration (see section 4.8).

There have been reports of hypokalaemia and renal failure (including fatalities). Some reports 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 chemotherapy and other medicines, symptoms or diseases or other predisposing conditions including advanced age), BINIT 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.

Hepatitis, hepatic failure

Cases of hepatic failure (including fatalities) have been reported during use of erlotinib. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medicines. Therefore, in such patients, periodic liver function testing should be considered. BINIT dosing should be interrupted if changes in liver function are severe (see section 4.8). BINIT is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation

Patients receiving BINIT are at increased risk of developing gastrointestinal perforation (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic medicines, corticosteroids, NSAIDs, and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. BINIT should be permanently discontinued in patients who develop gastrointestinal perforation (see section 4.8).

Bullous and exfoliative skin disorders

Bullous, 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 4.8). BINIT treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions. Patients with bullous and exfoliative skin disorders should be tested for skin infection and treated accordingly. For patients who are exposed to the sun, protective clothing, and/or use of sunscreen (mineral-containing) may be advisable.

Ocular disorders

Cases of corneal perforation or ulceration, uveitis, iridocyclitis and iritis have been reported during use of erlotinib (see section 4.8). 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. BINIT 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. BINIT therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain or when a diagnosis of ulcerative keratitis is confirmed.

Interactions with other medicines

Potent inducers of CYP3A4 may reduce the efficacy of BINIT whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of medicines should be avoided (see section 4.5)

Other forms of interactions

Erlotinib is characterised by a decrease in solubility at pH above 5. Medicines that alter the pH of the upper gastrointestinal (GI) tract, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of BINIT and hence its bioavailability. Increasing the dose of BINIT when co-administered with such medicines is not likely to compensate for the loss of exposure. Combination of BINIT with proton pump inhibitors should be avoided (see section 4.5). The effects of concomitant administration of BINIT with H2 antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided (see section 4.5). If the use of antacids are considered necessary during treatment with BINIT, they should be taken at least 4 hours before or 2 hours after the daily dose of BINIT.

BINIT contains sugar

BINIT contains lactose monohydrate. Patients with the rare hereditary condition of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BINIT.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

BINIT and other cytochrome P (CYP) substrates

BINIT 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.

When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure (area under the curve (AUC)) increased significantly by 39 %, while no statistically significant change in C_{max} was found. Similarly, the exposure to the active metabolite increased by about 60 % and 48 % for AUC and C_{max}, respectively. The clinical relevance of this increase has not been established. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g. fluvoxamine) are combined with BINIT. If adverse reactions related to BINIT are observed, the dose of BINIT may be reduced.

Pre-treatment or co-administration of BINIT did not alter the clearance of the prototypical CYP3A4 substrates, midazolam and erythromycin, but did appear to decrease the oral bioavailability of midazolam by up to 24 %. In another clinical study, erlotinib was shown not to affect pharmacokinetics of the concomitantly administered CYP3A4/2C8 substrate paclitaxel. Significant

interactions with the clearance of other CYP3A4 substrates are therefore unlikely.

The inhibition of glucuronidation may cause interactions with medicines 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 metabolism and increase plasma concentrations of BINIT. In a clinical study, the 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 (86 % of AUC and 69 % of C_{max}). Therefore, caution should be used when BINIT is combined with a potent CYP3A4 inhibitor, e.g. azole antifungals (i.e. ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary, the dose of BINIT should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase BINIT metabolism and significantly decrease its plasma concentrations. In a clinical study, the concomitant use of erlotinib and rifampicin (600 mg orally once daily for 7 days), a potent CYP3A4 inducer, resulted in a 69 % decrease in the median erlotinib AUC. Co-administration of rifampicin with a single 450 mg dose of BINIT resulted in a mean erlotinib exposure (AUC) of 57,5 % of that after a single 150 mg BINIT dose in the absence

of rifampicin treatment. Co-administration of BINIT with CYP3A4 inducers should therefore be avoided. For patients who require concomitant treatment with BINIT and a potent CYP3A4 inducer, such as rifampicin, an increase in dose to 300 mg should be considered while their safety (including renal and liver functions 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 with 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 BINIT. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

BINIT and coumarin-derived anticoagulants

Interaction with warfarin, leading to increased international normalised ratio (INR) and bleeding events, which in some cases were fatal, have been reported in patients receiving BINIT. Patients taking warfarin should be monitored regularly for any changes in prothrombin time or INR.

BINIT and statins

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

BINIT and smokers

Results of a pharmacokinetic interaction study indicated a significant 2,8-; 1,5- and 9-fold reduced AUC, C_{max} and plasma concentration at 24 hours, respectively, after administration of BINIT in smokers as compared to non-smokers (see section 5.2). Therefore, patients who are still smoking should be encouraged to stop smoking as early as possible before initiation of treatment with

BINIT, as plasma erlotinib concentrations are reduced otherwise. Based on data from clinical trials, no evidence was seen for any benefit of a higher erlotinib dose of 300 mg when compared with the recommended dose of 150 mg in active smokers. Safety data were comparable between the 300 mg and 150 mg doses; however, there was a numerical increase in the incidence of rash, interstitial lung disease and diarrhoea, in patients receiving the higher dose of erlotinib (see sections 4.2, 4.4 and 5.2).

BINIT and P-glycoprotein inhibitors

Erlotinib is a substrate for the P-glycoprotein (Pgp) active substance transporter. Concomitant administration of inhibitors of Pgp, e.g. ciclosporin and verapamil, may lead to altered distribution and/or altered elimination of BINIT. The consequences of this interaction for e.g. central nervous system (CNS) toxicity have not been established. Caution should be exercised in such situations.

BINIT and medicines altering pH

Erlotinib is characterised by a decrease in solubility at pH above 5. Medicines that alter the pH of the upper gastrointestinal (GI) tract may alter the solubility of BINIT and hence its bioavailability. Co-administration of BINIT with omeprazole, a proton pump inhibitor (PPI), decreased the erlotinib exposure (AUC) and maximum concentration (C_{max}) by 46 % and 61 %, respectively. There was no change to T_{max} or half-life. Concomitant administration of BINIT with 300 mg ranitidine, an H2-receptor antagonist, decreased erlotinib exposure (AUC) and maximum concentrations (C_{max}) by 33 % and 54 %, respectively. Increasing the dose of BINIT when co-administered with such medicines is not likely to compensate for this loss of exposure. However, when BINIT was dosed in a staggered manner 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure (AUC) and maximum concentrations (C_{max}) decreased only by 15 % and 17 %, respectively. The effect of antacids and H2 antagonists on the absorption of BINIT has not been investigated but absorption may be impaired, leading to lower plasma levels. Combination

of BINIT with proton pump inhibitors should be avoided (see section 4.4). If the use of ranitidine is considered, it should be used in a staggered manner; i.e. BINIT must be taken at least 2 hours before or 10 hours after ranitidine dosing. The ranitidine dose should be divided into 2 equal doses per day.

BINIT and gemcitabine

There were no significant effects of gemcitabine on the pharmacokinetics of erlotinib, nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine, in clinical studies.

BINIT and carboplatin/paclitaxel

BINIT increases platinum concentrations. In a clinical study, the concomitant use of erlotinib with carboplatin and paclitaxel led to an increase of total platinum AUC_{0-48} of 10,6 %. Although statistically significant, 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 BINIT.

BINIT and capecitabine

Capecitabine may increase BINIT concentrations. When erlotinib was given in combination with capecitabine, there was a statistically significant increase in erlotinib AUC and a borderline increase in C_{max} when compared with values observed in another study in which erlotinib was given as single treatment. There were no significant effects of erlotinib on the pharmacokinetics of capecitabine.

BINIT and proteasome inhibitors

Due to the working mechanism, proteasome inhibitors, including bortezomib, may be expected to

influence the effect of EGFR inhibitors including BINIT. Such influence is supported by limited clinical data and preclinical studies showing EGFR degradation through the proteasome.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential must be advised to avoid pregnancy while on BINIT. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy with BINIT. Women who are pregnant and/or breastfeeding should not receive BINIT.

Pregnancy

There are no studies in pregnant and/or breastfeeding women using BINIT. Studies in animals have shown no evidence of teratogenicity or abnormal parturition. However, an adverse effect on the pregnancy cannot be excluded as rat and rabbit studies have shown increased embryo/foetal lethality. The potential risk for humans is unknown.

Breastfeeding

It is not known whether BINIT is excreted in human milk. No studies have been conducted to assess the impact of BINIT 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 BINIT and for at least 2 weeks after the final dose.

Fertility

Studies in animals have shown no evidence of impaired fertility. However, an adverse effect on the fertility cannot be excluded as animal studies have shown effects on reproductive parameters. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. BINIT is not associated with impairment of mental ability. Caution is advised before driving a vehicle or operating machinery until the effects of BINIT are known.

4.8 Undesirable effects

Summary of the safety profile

The safety evaluation of erlotinib is based on the data from patients treated with at least one dose of erlotinib monotherapy and patients who received erlotinib in combination with gemcitabine.

The most frequent side effects seen in patients treated with erlotinib in clinical studies were rash and diarrhoea. Both rash and diarrhoea resulted in discontinuation of erlotinib in up to 1 % of patients. Dose modifications (interruptions or reductions) for rash and diarrhoea were needed in some of the patients.

In general, rash manifests as a mild or moderate erythematous and papulopustular rash, which may occur or worsen in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sunscreen (e.g. mineral containing) may be advisable. Skin fissures, mostly non-serious, were reported, most were associated with rash and dry skin.

Erlotinib plus gemcitabine was associated with a higher rate of certain class-specific side effects including rash and required more frequent dose reduction or interruption.

List of adverse reactions

Infections and infestations

Frequent: infection[1]

Metabolism and endocrine disorders

Frequent: anorexia, decreased weight

Psychiatric disorders

Frequent: depression

Nervous system disorders

Frequent: neuropathy, headache

Eye disorders

Frequent: keratoconjunctivitis sicca, conjuctivitis, keratitis

Less frequent: eyelash changes[2], corneal perforations and corneal ulcerations (have been reported as a complication of mucocutaneous inflammation, uveitis

Respiratory, thoracic and mediastinal disorders

Frequent: dyspnoea, cough, epistaxis

Less frequent: interstitial lung disease (ILD)[3]

Gastrointestinal disorders

Frequent: diarrhoea[7,8], nausea, vomiting, stomatitis, abdominal pain, dyspepsia, flatulence, gastrointestinal bleeding[4,7]

Less frequent: gastrointestinal perforations[7]

Hepatobiliary disorders

Frequent:	liver function test abnormalities[5]
Less frequent:	hepatic failure[6]

Skin and subcutateous tissue disorders

Frequent:	rash, pruritis, alopecia, dry skin, paronychia, folliculitis, acne/dermatitis acneiform, skin fissures
Less frequent:	hirsutism, eyebrow changes, brittle and loose nails, mild skin reactions such as hyperpigmentation, palmar plantar erythrodysaesthesia syndrome, Stevens-Johnson syndrome/toxic epidermal necrolysis[7]

Musculoskeletal and connective tissue disorders

Frequent:	rigors

Renal and urinary disorders

Frequent:	renal insufficiency
Less frequent:	nephritis, proteinuria

General disorders and administration site conditions

Frequent:	fatigue, pyrexia

[1] Severe infections, with or without neutropenia, have included pneumonia, sepsis and cellulitis.

[2] Including in-growing eyelashes, excessive growth and thickening of the eyelashes.

[3] Including fatalities, in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumours (see section 4.4).

[4] In clinical studies, some cases have been associated with concomitant warfarin administration

and some with concomitant nonsteroidal anti-inflammatory drug (NSAID) administration (see section 4.5).

[5] Including increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. Cases were mainly mild to moderate in severity, transient in nature or associated with liver metastases.

[6] Including fatalities. Confounding factors included pre-existing liver disease or concomitant hepatotoxic medications (see section 4.4).

[7] Including fatalities (see section 4.4)

[8] Can lead to dehydration, hypokalaemia and renal failure.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BINIT is important. It allows continued monitoring of the benefit/risk balance of BINIT. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Single oral doses of BINIT up to 1 000 mg in healthy subjects, and up to 1 600 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 reactions such as diarrhoea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose.

Management

In case of suspected overdose, BINIT should be withheld, and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor.

ATC code: L01XE03.

Mechanism of action

Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known as HER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR 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.

EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signalling in these EGFR mutation positive tumours is attributed to the tight binding of erlotinib to the ATP-binding site in the mutated kinase domain of the EGFR. Due to the blocking of downstream-signaling, the proliferation of cells is stopped, and cell death is induced through the intrinsic apoptotic pathway. Tumour regression is observed in mouse models of enforced expression of these EGFR activating mutations.

5.2 Pharmacokinetic properties

Absorption

After oral administration, erlotinib peak plasma levels are obtained in approximately 4 hours after

oral dosing. A study in normal healthy volunteers provided an estimate of the absolute bioavailability of 59 % compared to intravenous (IV) administration. The exposure after an oral dose may be increased by food.

Distribution

Erlotinib has a mean apparent volume of distribution of 232 L and distributes into tumour tissue of humans. In a study of 4 patients (3 with NSCLC and 1 with laryngeal cancer) receiving 150 mg daily oral doses of erlotinib, tumour samples from surgical excisions on day 9 of treatment revealed tumour concentrations of erlotinib that averaged 1,185 ng/g of tissue. This corresponded to an overall average of 63 % (range 5 – 161 %) of the steady state observed peak plasma concentrations. The primary active metabolites were present in tumour at concentrations averaging 160 ng/g tissue, which corresponded to an overall average of 113 % (range 88 – 130 %) of the observed steady state peak plasma concentrations. 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 % at the recommended dose. 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 µg•hr/mL.

Biotransformation

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 1B1 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 OSI-420 and OSI-413 of erlotinib produced
by O-demethylation of either side chain have comparable potency to erlotinib in non-clinical *in vitro* assays and *in vivo* tumour models. They are present in plasma at levels that are < 10 % of erlotinib and display similar pharmacokinetics as erlotinib.

Elimination

Erlotinib is excreted predominantly as metabolites via the faeces (> 90 %) with renal elimination accounting for only a small amount (approximately 9 %) of an oral dose. Less than 2 % of the orally administered dose is excreted as parent substance. A population pharmacokinetic analysis in 591 patients receiving single treatment with erlotinib shows 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.

A second population pharmacokinetic analysis was conducted that incorporated erlotinib data from 204 pancreatic cancer patients who received erlotinib plus gemcitabine. This analysis demonstrated that covariants affecting erlotinib clearance in patients from the pancreatic study were very similar to those seen in the prior single treatment pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

Pharmacokinetics in special populations

Based on population pharmacokinetic analysis, no clinically significant relationship between predicted apparent clearance and patient age, bodyweight, gender and ethnicity were observed. Patient factors, which correlated with erlotinib pharmacokinetics, were serum total bilirubin, AAG and current smoking. Increased serum concentrations of total bilirubin and AAG concentrations were associated with a reduced erlotinib clearance. The clinical relevance of these differences is unclear. However, smokers had an increased rate of erlotinib clearance.

Smokers

A pharmacokinetic study in non-smoking and currently cigarette smoking healthy subjects has shown that cigarette smoking leads to increased clearance of, and decreased exposure to, erlotinib.

This reduced exposure in current smokers is presumably due to induction of CYP1A1 in lung and CYP1A2 in the liver.

In clinical studies current smokers achieved erlotinib steady state trough plasma concentration of 0,65 µg/mL (n=16) which was approximately 2-fold less than the former smokers or patients who had never smoked (1,28 µg/mL, n=108). This effect was accompanied by a 24 % increase in apparent erlotinib plasma clearance. In NSCLC patients who were current smokers, pharmacokinetic analyses at steady-state indicated a dose proportional increase in erlotinib exposure when the erlotinib dose was increased from 150 mg to the maximum tolerated dose of 300 mg. Steady-state trough plasma concentrations at a 300 mg dose in current smokers in clinical studies was 1,22 µg/mL (n=17) (see sections 4.2, 4.4 and 4.5).

Based on the results of pharmacokinetic studies, current smokers should be advised to stop smoking while taking BINIT, as plasma concentrations could be reduced otherwise.

Based on population pharmacokinetic analysis, the presence of an opioid appeared to increase

exposure by about 11 %.

Elderly population

There have been no specific studies in elderly patients.

Hepatic impairment

Erlotinib is primarily cleared by the liver. In patients with solid tumours and with moderately impaired hepatic function (Child-Pugh score 7 – 9), geometric mean erlotinib AUC_{0-t} and C_{max} was 27 000 ng•h/mL and 805 ng/mL, respectively, as compared to 29 300 ng•h/mL and 1 090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the C_{max} was statistically significant lower in moderately hepatic impaired patients, this difference is not considered clinically relevant. No data are available regarding the influence of severe hepatic dysfunction on the pharmacokinetics of erlotinib. In population pharmacokinetic analysis, increased serum concentrations of total bilirubin were associated with a slower rate of erlotinib clearance.

Renal impairment

Erlotinib and its metabolites are not significantly excreted by the kidney, as less than 9 % of a single dose is excreted in the urine. In population pharmacokinetic analysis, no clinically significant relationship was observed between erlotinib clearance and creatinine clearance, but there are no data available for patients with creatinine clearance < 15 mL/min.

Paediatric population

There have been no specific studies in peadiatric patients.

5.3. Preclinical safety data

No information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica (E551)

Hypromellose (E464)

Lactose monohydrate

Magnesium stearate (E572)

Microcrystalline cellulose (E460)

Opadry® white (containing hypromellose (E464), macrogol (E1521), talc (E553b) and titanium dioxide (E171))

Polyvinylpolypyrrolidone (E1202)

Sodium lauryl sulphate (E487).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strip(s) in the outer carton until required for use.

6.5 Nature and contents of container

Silver OPA/Aluminium/PVC and aluminium blister strips packed in a cardboard carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion, Pretoria

0157

8. REGISTRATION NUMBERS

BINIT 25: 54/26/0826

BINIT 100: 54/26/0827

BINIT 150: 54/26/0828

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 August 2022

10. DATE OF REVISION OF THE TEXT

Date of approval: 23 August 2022