SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TARSINIB 150 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Active substance:

Erlotinib hydrochloride ..... 163.92 mg (equivalent to 150 mg erlotinib)

Excipients with known effect:

Lactose monohydrate (Pharmatose 200 M) (from cow's milk) ..... 106.28 mg
Sodium starch glycolate (Primogel) ..... 40.8 mg
Sodium lauryl sulfate (SLS) ..... 14.4 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White, biconvex, round film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC):

TARSINIB is indicated for the first-line treatment of metastatic non-squamous non-small cell lung cancer patients with epidermal growth factor receptor (EGFR) exon 19 deletion and/or exon 21 (L858R) mutation, confirmed in an accredited laboratory. It is also indicated for second-line treatment in patients with the above-defined mutations and deletions in non-squamous NSCLC who have experienced progression following first-line chemotherapy, until disease progression.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

TARSINIB therapy should be initiated by a physician experienced in the use of anti-cancer therapies.

Standard dose in non-small cell lung cancer unless recommended otherwise by the doctor:

Before starting TARSINIB treatment in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have not received first-line chemotherapy, an EGFR mutation test should be performed.

The recommended daily dose of TARSINIB is 150 mg, to be taken at least one hour before or two hours after meals.

Method of administration:

Oral use.

Additional information on special populations:

When dose adjustment is necessary, it is recommended to reduce the dose in 50 mg steps (see section 4.4).

Dose adjustments may also be required when used concurrently with CYP3A4 substrates and modulators (see section 4.5).

Hepatic impairment:
Erlotinib is primarily metabolized in the liver and excreted in bile. While patients with mild hepatic impairment (Child-Pugh score 7–9) exhibit similar erlotinib clearance compared to those with normal liver function, caution should be exercised when administering TARSINIB to patients with hepatic impairment. If severe adverse events occur, dose reduction or interruption of TARSINIB treatment should be considered. The safety and efficacy of erlotinib have not been studied in patients with severe hepatic impairment (AST/SGOT and ALT/SGPT levels > 5 x upper limit of normal). TARSINIB should not be used in patients with total bilirubin levels three times above the upper limit of normal (see sections 4.4 and 5.2).

Renal impairment:
The safety and efficacy of erlotinib in patients with renal impairment (serum creatinine concentration >1.5 x upper limit of normal) have not been studied. Based on pharmacokinetic studies, no dose adjustment is required for patients with mild to moderate renal impairment (see section 5.2). TARSINIB is not recommended for use in patients with severe renal impairment.

Pediatric population:
The safety and efficacy of erlotinib in patients under 18 years of age have not been studied. Its use in pediatric patients is not recommended.

Geriatric population:
The safety and efficacy of erlotinib in elderly patients have not been studied.

Smokers:
Smoking has been shown to reduce erlotinib exposure by 50–60%. In current smokers with non-small cell lung cancer (NSCLC), the maximum tolerable dose of TARSINIB is 300 mg.

In patients who continue smoking, a 300 mg dose has not demonstrated increased efficacy compared to the recommended 150 mg dose for second-line treatment following failed chemotherapy. Safety data are comparable between the 300 mg and 150 mg doses; however, patients receiving the higher dose exhibited a numerical increase in incidences of rash, interstitial lung disease, and diarrhea. Patients who smoke should be encouraged to quit smoking (see sections 4.4, 4.5, 5.1, and 5.2).

4.3 Contraindications
TARSINIB is contraindicated in cases of hypersensitivity to erlotinib or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
Determination of EGFR mutation status
When considering erlotinib for first-line treatment of locally advanced or metastatic NSCLC, it is important to determine the patient's EGFR mutation status.

A validated, reliable, sensitive, and robust test with pre-defined positivity thresholds should be used to identify EGFR mutation status. This can be conducted using tumor DNA obtained from tissue samples or circulating free DNA (cfDNA) from blood (plasma) samples.

If plasma-based cfDNA testing is used and results are negative for activating mutations, a tissue test should be performed whenever possible, as false-negative results are more likely with plasma-based testing.

Smokers
Due to lower plasma concentrations of erlotinib observed in smokers compared to non-smokers, patients who smoke are advised to quit. The clinical significance of the decrease in plasma concentration is expected to be meaningful (see sections 4.2, 4.5, 5.1, and 5.2).

Interstitial Lung Disease (ILD)
Very rare cases of interstitial lung disease (ILD)-like events, some of which have been fatal, have been reported in patients receiving erlotinib for the treatment of NSCLC. In the BR.21 phase III trial, the incidence of serious ILD-like events was 0.8% in both the placebo and erlotinib groups.

A meta-analysis of randomized controlled clinical trials (excluding phase I and single-arm phase II studies due to the absence of control groups) reported an incidence of ILD-like events of 0.9% in the erlotinib group and 0.4% in the control group.

Reported diagnoses in patients suspected of having ILD-like events include pneumonia, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonitis, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome (ARDS), lung infiltration, and alveolitis. These symptoms have occurred between a few days and several months after starting erlotinib treatment. Confounding factors such as concurrent or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections have been commonly observed. Studies conducted in Japan have shown a higher incidence of ILD (approximately 5% with a 1.5% mortality rate).

In patients who develop sudden onset, new, and/or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever, TARSINIB treatment should be interrupted until diagnostic evaluations are completed. If interstitial lung disease (ILD) is diagnosed, TARSINIB treatment should be discontinued, and appropriate treatment should be initiated (see section 4.8).

Diarrhea, dehydration, electrolyte imbalance, renal failure
Approximately 50% of patients using erlotinib have experienced diarrhea, including rare cases that were fatal. Moderate to severe diarrhea should be treated with loperamide. In some cases, dose reduction may be required. In clinical trials, dose reductions were performed in 50 mg increments. Dose reductions in 25 mg increments have not been studied. In cases of severe or persistent diarrhea, nausea, anorexia, or vomiting accompanied by dehydration, TARSINIB treatment should be discontinued, and measures to treat dehydration should be implemented (see section 4.8). Hypokalemia and cases of acute renal failure (some of which were fatal) have been reported rarely. Some renal failures occurred alongside concurrent chemotherapy, while others were secondary to dehydration caused by diarrhea, vomiting, and/or anorexia. In cases of more severe or persistent diarrhea or dehydration, particularly in patients with risk factors that exacerbate these conditions (such as concurrent chemotherapy or other medications, symptoms or illnesses, or advanced age), TARSINIB treatment should be discontinued. Patients should be intensively rehydrated intravenously. Additionally, in patients at risk of dehydration, renal function and serum electrolytes, including potassium, should be monitored periodically.

Hepatotoxicity
Cases of drug-induced severe liver damage, including hepatitis, acute hepatitis, and liver failure (including fatalities), have been reported during erlotinib treatment. Risk factors

include pre-existing liver disease or concomitant use of hepatotoxic drugs. Periodic liver function tests are recommended during TARSINIB treatment. In patients with pre-existing liver failure or biliary obstruction, liver function monitoring frequency should be increased. Patients reporting symptoms indicative of liver damage should undergo prompt clinical evaluation and liver function tests. If liver function changes are severe, TARSINIB dosage should be interrupted (see section 4.8). The use of TARSINIB in patients with severe hepatic dysfunction is not recommended.

Gastrointestinal Perforation
The risk of developing gastrointestinal perforation is high in patients using TARSINIB, which is uncommon but can be fatal in some cases. The risk is higher in patients receiving concurrent treatment with antiangiogenic drugs, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or those with a history of peptic ulceration or diverticular disease. In patients who develop gastrointestinal perforation, TARSINIB treatment should be permanently discontinued (see section 4.8).

Bullous or Exfoliative Skin Diseases
Rare cases, some of which can be fatal, of bullous, raised, and exfoliative skin disorders suggestive of Steven Johnson syndrome/toxic epidermal necrolysis have been reported (see section 4.8). If patients develop severe bullous, raised, or exfoliative skin disorders, treatment with TARSINIB should be discontinued or interrupted. Patients with bullous and exfoliative skin disorders should be tested for skin infections and treated according to local treatment guidelines.

Ocular Diseases
In the case of symptoms indicating acute or worsening keratitis, such as eye inflammation, lacrimation, photophobia, blurred vision, eye pain, and/or redness, immediate consultation with an ophthalmologist is recommended. If ulcerative keratitis is diagnosed, TARSINIB treatment should be interrupted or discontinued. If keratitis is diagnosed, a careful risk-benefit assessment should be made to determine whether to continue treatment. TARSINIB should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eyes. Contact lenses are a risk factor for keratitis and ulceration. Very rare cases of corneal perforation or ulceration have been reported during erlotinib use (see section 4.8).

Drug Interactions
Potent inducers of CYP3A4 may reduce the effectiveness of TARSINIB, while potent inhibitors of CYP3A4 may increase toxicity. Co-administration of these types of agents should be avoided (see section 4.5)

Other Interaction Forms
Erlotinib is characterized by decreased solubility at pH levels higher than 5. Medical products that alter the pH of the upper gastrointestinal system, such as proton pump inhibitors, H_2 antagonists, and antacids, can alter the solubility and, consequently, the bioavailability of erlotinib. When used together with these products, increasing the TARSINIB dose will not compensate for the reduced exposure. Co-administration of erlotinib with proton pump inhibitors should be avoided. The effect of erlotinib with H_2 antagonists and antacids is unknown, but reduced bioavailability is expected. Therefore, co-use of these combinations should be avoided (see section 4.5). If antacid use is necessary during TARSINIB therapy, it should be taken at least 4 hours before or 2 hours after the daily TARSINIB dose.

Other
TARSINIB should not be used in patients who have previously used any EGFR pathway inhibitors.

Known Excipients:
TARSINIB contains lactose monohydrate. Patients with rare hereditary galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not use this medication.

This medicine contains less than 1 mmol of sodium (23 mg) per tablet, i.e., essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction
Interaction studies have been conducted only in adults.

Erlotinib and Other CYP Substrates:
Erlotinib is a potent inhibitor of CYP1A1, a moderate inhibitor of CYP3A4 and CYP2C8, and a strong inhibitor of *in vitro* UGT1A1-mediated glucuronidation. The physiological relevance of the strong inhibition of CYP1A1 is not well understood due to the very limited expression of CYP1A1 in human tissues.

When erlotinib is co-administered with ciprofloxacin, a moderate inhibitor of CYP1A2, erlotinib exposure [AUC] increased significantly by 39%, while no statistically significant changes in maximum concentration (C_{max}) were observed. Similarly, exposure to the active metabolite increased by approximately 60% and 48% for AUC and C_{max}, respectively. The clinical significance of these increases has not been determined. Caution should be exercised when ciprofloxacin or potent CYP1A2 inhibitors (e.g., fluvoxamine) are combined with erlotinib. If adverse reactions related to erlotinib are observed, the erlotinib dose may be reduced.

Pre-treatment or co-administration of erlotinib did not affect the clearance of the prototype CYP3A4 substrates midazolam and erythromycin, but it was found to reduce the oral bioavailability of midazolam by up to 24%. In another clinical study, it was shown that co-administered erlotinib did not affect the pharmacokinetics of the CYP3A4/2C8 substrate paclitaxel. Therefore, significant interactions with the clearance of other CYP3A4 substrates are unlikely.

Inhibition of glucuronidation may lead to interactions with medical products that are substrates of UGT1A1 and are eliminated exclusively through this pathway. Patients with low UGT1A1 expression levels or genetic glucuronidation disorders (e.g., Gilbert's syndrome) may experience increased serum bilirubin concentrations, and these patients should be treated with caution.

Erlotinib is metabolized in humans in the liver by hepatic cytochromes, primarily CYP3A4 and, to a lesser extent, CYP1A2. Additionally, extrahepatic metabolism performed by CYP3A4 in the intestines, CYP1A1 in the lungs, and CYP1B1 in tumor tissue contributes to the metabolic clearance of erlotinib. Potential interactions may arise with drugs metabolized by these enzymes or inhibitors or inducers of these enzymes.

Potent inhibitors of CYP3A4 reduce the metabolism of erlotinib and increase its plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally twice daily for 5 days) led to increased exposure to erlotinib (an 86% increase in median erlotinib exposure

[AUC] and a 69% increase in C_{max} compared to erlotinib alone). Therefore, caution should be exercised when erlotinib is combined with azole antifungals (i.e., ketoconazole, itraconazole, voriconazole), protease inhibitors, erythromycin, or clarithromycin, which are potent CYP3A4 inhibitors. If necessary, particularly if toxicity is observed, the erlotinib dose should be reduced.

Potent inducers of CYP3A4 increase the metabolism of erlotinib and significantly reduce its plasma concentrations. In a clinical study, co-administration of erlotinib and rifampicin, a strong CYP3A4 inducer (600 mg orally once daily for 7 days), resulted in a 69% decrease in median erlotinib AUC levels. Co-administration of rifampicin (450 mg) with a single dose of erlotinib led to an average exposure (AUC) of 57.5% of the level observed with a 150 mg dose of erlotinib without rifampicin treatment. Therefore, co-administration of erlotinib with CYP3A4 inducers should be avoided. In cases where co-administration with a strong CYP3A4 inducer like rifampicin is necessary, close monitoring of safety (including renal and liver function and serum electrolytes) should be performed, and the dose may be increased up to 300 mg. If well tolerated for more than two weeks, a further increase to 450 mg may be considered with close safety monitoring. Other inducers, such as phenytoin, carbamazepine, barbiturates, or St. John's Wort (*Hypericum perforatum*), may also decrease exposure levels. Caution should be exercised when combining these substances with erlotinib, and alternative treatment options without strong CYP3A4 inducing activity should be considered when possible.

Erlotinib and Coumarin-Derivative Anticoagulants:
Interactions with coumarin-derivative anticoagulants, including warfarin, have been reported in patients receiving erlotinib, leading to elevated International Normalized Ratio (INR) and, in some cases, fatal bleeding events. Patients on coumarin-derivative anticoagulants should be regularly monitored for changes in prothrombin time or INR.

Erlotinib and Statins:
Combining erlotinib with a statin may increase the potential for statin-induced myopathy, including the rare occurrence of rhabdomyolysis.

Erlotinib and Smokers:
A pharmacokinetic interaction study showed that in smokers, erlotinib administration resulted in significant reductions in AUC_{inf}, C_{max}, and plasma concentrations after 24 hours, compared to non-smokers, with decreases of 2.8, 1.5, and 9 times, respectively. Therefore, patients who currently smoke should be encouraged to quit smoking as soon as possible before starting treatment with erlotinib, as plasma erlotinib concentrations may decrease otherwise.

Data from the CURRENTS study did not provide any evidence suggesting that a higher dose of erlotinib (300 mg) offers any additional benefit compared to the recommended 150 mg dose in smokers. Safety data can be compared between the 300 mg and 150 mg doses, but a numerical increase in the incidence of rash, interstitial lung disease, and diarrhea was observed in patients receiving the higher dose (refer to Sections 4.2, 4.4, 5.1, and 5.2).

Erlotinib and P-Glycoprotein Inhibitors:
Erlotinib is a substrate for the P-glycoprotein (P-gp) efflux transporter. Co-administration with P-gp inhibitors (e.g., cyclosporine and verapamil) may alter the distribution and/or elimination of erlotinib. The consequences of this interaction, such as central nervous system (CNS) toxicity, have not been determined. Caution should be exercised in these situations.

Erlotinib and pH-Altering Medications:
Erlotinib has reduced solubility at pH levels above 5. Medications that alter the pH of the upper gastrointestinal tract may affect the solubility and consequently the bioavailability of erlotinib. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, reduced erlotinib exposure (AUC) and maximum concentration (C_{max}) by 46% and 61%, respectively. There was no change in Tmax or half-life. Similarly, co-administration of erlotinib with 300 mg ranitidine, an H2 receptor antagonist, reduced erlotinib exposure (AUC) and C_{max} by 33% and 54%, respectively. Increasing the erlotinib dose to compensate for this loss in exposure may not be effective. However, when erlotinib is administered at 150 mg twice daily, 2 hours before or 10 hours after ranitidine, the reduction in exposure (AUC) and C_{max} is only 15% and 17%, respectively. The effect of antacids on erlotinib absorption has not been studied, but they may lead to decreased plasma levels due to impaired absorption. In summary, co-administration of erlotinib with proton pump inhibitors should be avoided. If antacids are considered during erlotinib treatment, they should be taken at least 4 hours before or 2 hours after the daily dose of erlotinib. If ranitidine is considered, it should be taken at separate times, specifically at least 2 hours before or 10 hours after the dose of erlotinib.

Erlotinib and Gemcitabine:
In a Phase Ib study, no significant effect of gemcitabine on erlotinib pharmacokinetics or erlotinib on gemcitabine pharmacokinetics was observed.

Erlotinib and Carboplatin/ Paclitaxel:
Erlotinib increases platinum concentrations. In a clinical study, the co-administration of erlotinib with carboplatin and paclitaxel led to a 10.6% increase in total platinum AUC_{0-48}. Although statistically significant, this difference is not considered clinically meaningful. In clinical practice, other co-factors, such as renal insufficiency, may increase carboplatin exposure. There is no significant effect of carboplatin or paclitaxel on the pharmacokinetics of erlotinib.

Erlotinib and Capecitabine:
Capecitabine may increase erlotinib concentrations. Compared to a study where erlotinib was administered alone, co-administration with capecitabine led to a statistically significant increase in erlotinib AUC, with C_{max} showing a borderline increase. There is no significant effect of erlotinib on the pharmacokinetics of capecitabine.

Erlotinib and Proteasome Inhibitors:
Based on their mechanism of action, proteasome inhibitors, including bortezomib, may alter the effects of EGFR inhibitors like erlotinib. This change is supported by limited clinical data and preclinical studies showing EGFR degradation via the proteasome.

Additional Information on Special Populations:
No interaction studies have been conducted in special populations.

Pediatric Population:
No interaction studies with erlotinib have been conducted in patients under 18 years of age.

4.6 Fertility, pregnancy and lactation
General principles
Pregnancy category “D”.

Women of childbearing potential / Birth control (Contraception)
Women with childbearing potential should be advised to avoid becoming pregnant while taking TARSINIB. Adequate contraceptive methods must be used during treatment and for at least two weeks following its completion.

Pregnancy
There is insufficient data on the use of erlotinib in pregnant women. Animal studies have not shown teratogenicity or abnormal parturition. However, potential adverse effects on pregnancy cannot be ruled out, as increased embryo/fetal lethality was observed in rabbits and rats (see section 5.3). The potential risk to humans is unknown. TARSINIB should not be used during pregnancy unless clearly necessary. Treatment in pregnant women should only continue if the expected benefits to the mother outweigh the potential risks to the fetus.

Breastfeeding
It is unknown whether erlotinib passes into human milk. No studies have been conducted to assess its effects on milk production or its presence in breast milk. Due to the unknown potential harm to infants, mothers should be advised not to breastfeed while using TARSINIB and for at least two weeks after the last dose.

Reproduction ability / Fertility
Animal studies have not shown fertility disorders. However, as effects on reproductive parameters were observed in animal studies, adverse effects on fertility cannot be excluded (see section 5.3). The potential risk to humans is unknown.

4.7 Effects on ability to drive and use machines
No studies have been conducted regarding the effects on driving or operating machines. However, erlotinib is not associated with impairment of mental abilities.

4.8 Undesirable effects
Summary of the Safety Profile
The safety assessment of erlotinib is based on data from 1,500 patients who received at least one 150 mg dose as monotherapy and 300 patients who received 100 mg or 150 mg of erlotinib in combination with gemcitabine.

Non-Small Cell Lung Cancer (NSCLC)
(TARSINIB is used as monotherapy.)

First-Line Treatment of EGFR-Mutated Patients
The safety of erlotinib as a first-line treatment for NSCLC patients with EGFR-activating mutations was evaluated in 75 patients in an open-label, randomized, Phase III ML20650 study conducted with 154 patients.

In Study ML20650, the most common adverse effects observed in patients treated with erlotinib were rash and diarrhea. Most cases were Grade 1 or Grade 2 in severity and managed without intervention. Information on the incidence and grades of rash and diarrhea across all clinical studies is available in the "Description of Selected Adverse Effects" section below.

Maintenance Therapy

In two other double blind, randomized, placebo-controlled Phase III studies, BO18192 (SATURN) and BO25460 (IUNO), erlotinib was administered as maintenance therapy after first-line chemotherapy. These studies involved a total of 1,532 patients with advanced, recurrent, or metastatic NSCLC following first-line standard platinum-based chemotherapy.

In the BO18192 and BO25460 studies, the most common adverse reactions in patients treated with erlotinib were rash and diarrhea.

Second-Line and Advanced Treatment

In a randomized, double-blind study (BR.21; where erlotinib was applied as a second-line treatment), rash and diarrhea were the most frequently reported adverse reactions. Most were Grade 1 or Grade 2 in severity and resolved without intervention. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

Summary of Adverse Reactions in Tabular Form

The incidence of adverse reactions (ADRs) reported in clinical trials and post-marketing settings in patients receiving erlotinib as monotherapy or in combination with chemotherapy is summarized in Table 1.

Adverse effects are categorized according to the MedDRA organ system. The following terms are used to rank the frequencies of adverse effects: Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Within each frequency groups, adverse reactions are presented in decreasing order of severity.

Table 1: Summary of Adverse Effects from Clinical Studies and Post-Marketing Settings by Frequency

Infections and Infestations	
Very Common	Infection*
Metabolism and Nutrition Disorders	
Very Common	Anorexia, weight loss
Psychiatric Disorders	
Very Common	Depression
Nervous System Disorders	
Very Common	Neuropathy, headache
Eye Disorders	
Very Common	Keratoconjunctivitis sicca
Common	Keratitis, conjunctivitis
Uncommon	Eyelash changes*
Very Rare	Corneal perforations, corneal ulceration, uveitis
Respiratory, Thoracic, and Mediastinal Disorders	
Very Common	Dyspnea, cough
Common	Epistaxis
Uncommon	Interstitial lung disease*
Gastrointestinal Disorders	
Very Common	Diarrhea*, nausea, vomiting, stomatitis, abdominal pain, dyspepsia, flatulence
Common	Gastrointestinal bleeding*
Uncommon	Gastrointestinal perforations*
Rare	Pneumatosis intestinalis

Hepatobiliary Disorders	
Very Common	Abnormal liver function tests
Rare	Liver failure
Not known (cannot be estimated from the available data)	Acute hepatitis
Skin and Subcutaneous Tissue Disorders	
Very Common	Rash*, pruritus
Common	Alopecia, dry skin, paronychia, folliculitis, acne/acne-like dermatitis, skin fissures
Uncommon	Mild skin reactions such as hirsutism, eyebrow changes, nail brittleness and loss, hyperpigmentation
Rare	Palmar-plantar erythrodysesthesia syndrome
Very Rare	Stevens-Johnson syndrome/Toxic epidermal necrolysis*
Renal and Urinary Disorders	
Common	Renal failure
Uncommon	Nephritis, proteinuria
General Disorders and Conditions at the Administration Site	
Very Common	Fatigue, hot flashes, chills

*For detailed information, refer to the "Description of Selected Adverse Reactions" section.

Description of Selected Adverse Reactions

Rash

Rash includes acneiform dermatitis. Typically, rash manifests as mild to moderate erythematous and papulopustular eruptions that may occur or worsen in sun-exposed areas. For patients exposed to sunlight, the use of protective clothing and/or sunscreen (e.g., mineral-based) may be recommended.

Diarrhea

Diarrhea can lead to dehydration, hypokalemia, and renal failure. Fatal cases have also been reported (see section 4.4).

Table 2: Summary of Rash and Diarrhea Incidence and Grades Observed in Each Clinical Study

Study	Indication	Rash (%)					Diarrhea (%)				
		Grade			Actions Taken		Grade			Actions Taken	
		None	3	4	Discontinuation	Mode[1]	None	3	4	Discontinuation	Mode[1]
ML20650	NSCLC	80	9	0	1	11	57	4	0	1	7
BO18192	NSCLC	49.2	6	0	1	8.3	20.3	1.8	0	<1	3
BO25460	NSCLC	39.4	5	0	0	5.6	24.2	2.5	0	0	2.8
BR.21	NSCLC	75	9		1	6	54	6		1	1
PA.3	Pancreatic cancer	-	5		1	2	-	5		1	2

[1] Dose modification

Infections

This may include severe infections such as pneumonia, sepsis, and cellulitis, with or without neutropenia.

Eyelash Changes

Changes include non-growth, excessive growth, and thickening of eyelashes.

Interstitial Lung Disease (ILD)
ILD includes fatalities in patients receiving erlotinib for the treatment of NSCLC or other advanced solid tumors (see section 4.4). A higher incidence has been observed in patients from Japan (see section 4.4)

Gastrointestinal (GI) Bleeding
GI bleeding includes cases with fatal outcomes (see section 4.4). In clinical studies, some cases were associated with concomitant use of warfarin, and others with NSAID use (see section 4.5). Gastrointestinal perforations also include fatalities (see section 4.4).

Liver Function Test Abnormalities
Abnormalities include increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin. Cases have mostly been mild to moderate, transient in nature, or associated with liver metastases.

Liver Failure
This includes fatalities. Risk factors may include pre-existing liver disease or concomitant hepatotoxic medications (see section 4.4).

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis
This also includes fatalities (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose
Symptoms:
Single oral doses of up to 1000 mg in healthy individuals and up to 1600 mg in cancer patients have been tolerated. However, doses of 200 mg administered twice daily in healthy volunteers were not well tolerated, even after a few days of administration. Based on the data from these studies, severe adverse events such as diarrhea, rash, and possible elevation of liver transaminases may occur at doses higher than the recommended dose.

Management:
In case of suspected overdose, TARSINIB should be discontinued, and symptomatic treatment should be initiated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group **:** Antineoplastic agents, protein kinase inhibitors, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors
ATC code **:** L01EB02

Mechanism of Action:
Erlotinib is an inhibitor of the epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR, also known as HER1). It effectively inhibits the intracellular phosphorylation of EGFR. The EGFR/HER1 receptor is expressed on the surface of normal and cancer cells. In preclinical models, inhibition of EGFR phosphorylation results in cell stasis and/or death.

EGFR mutations can lead to constitutive activation of anti-apoptotic and proliferative signaling pathways. The potent effect of erlotinib in inhibiting EGFR-mediated signaling in tumors with EGFR mutations is attributed to its strong binding to the ATP-binding site within the mutant kinase region of EGFR. Due to the inhibition of downstream signaling, cell proliferation is halted, and cell death is initiated through the intrinsic apoptotic pathway. Tumor regression has been observed in mouse models where the expression of these activating EGFR mutations was triggered.

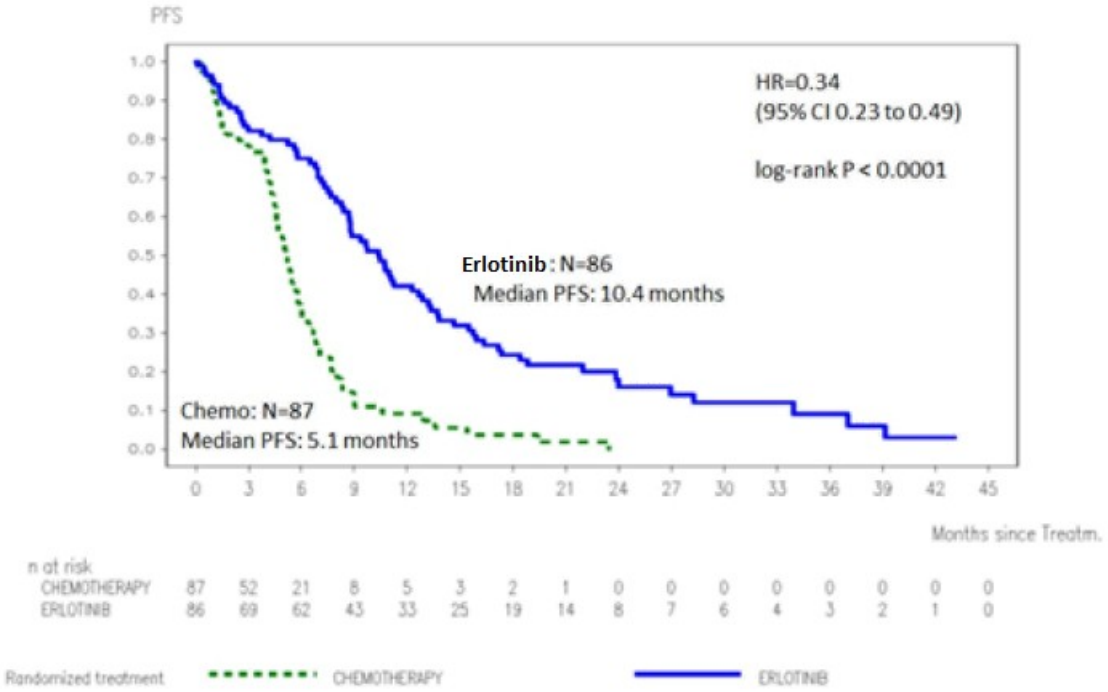
Clinical Efficacy

First-line treatment of non-small cell lung cancer (NSCLC) with EGFR-activating mutations (administration of TARSINIB as monotherapy)

The efficacy of erlotinib as a first-line treatment in patients with NSCLC and EGFR-activating mutations was demonstrated in a phase III, randomized, open-label study (ML20650, EURTAC). This study was conducted in Caucasian patients with metastatic or locally advanced (stages IIIB and IV) NSCLC who had not previously received chemotherapy or systemic antitumor therapy for advanced disease and had mutations in the tyrosine kinase region of EGFR (exon 19 deletions or exon 21 mutations). Patients were randomized in a 1:1 ratio to receive either daily 150 mg erlotinib or four cycles of platinum-based doublet chemotherapy.

The primary endpoint was progression-free survival (PFS) as assessed by the investigator. Efficacy results are provided in Table 3.

Figure 1: Kaplan-Meier curve for Progression-Free Survival (PFS) assessed by the investigator in the ML20650 (EURTAC) study (cut-off April 2012)



HR: Hazard Ratio, CI: Confidence Interval, PFS: Progression-Free Survival

Table 3: Efficacy results of erlotinib compared to chemotherapy in the ML20650 (EURTAC) study

		Erlotinib	Chemotherapy	Hazard Ratio (95% CI)	p-value
Pre-planned interim analysis (35% OS maturity) (n=153) Cut-off date: Aug 2010		n=77	n=76		
	Primary endpoint: Progression-Free Survival (PFS, median in months) * Investigator Assessed **	9,4	5,2	0,42 [0,27-0,64]	p<0,0001
	Independent Review **	10,4	5,4	0,47 [0,27-0,78]	p=0,003
	Best Overall Response Rate (CR/PR)	%54,5	%10,5		p<0,0001
	Overall Survival (OS) (months)	22,9	18,8	0,8 [0,47-1,37]	p=0,417
Research-specific analysis (40% OS maturity) (n=173) Cut-off date: Jan 2011		n=86	n=87		
	PFS (median in months), Investigator Assessed	9,7	5,2	0,37 [0,27-0,54]	p<0,0001
	Best Overall Response Rate (CR/PR)	%58,1	%14,9		p<0,0001
	OS (months)	19,3	19,5	1,04 [0,65-1,68]	p=0,8702
Updated analysis (62% OS maturity) (n=173) Cut-off date: April 2012		n=86	n=87		
	PFS (median in months)	10,4	5,1	0,34 [0,23-0,49]	p<0,0001
	OS*** (months)	22,9	20,8	0,93 [0,64-1,36]	p=0,7149

CR = Complete Response; PR = Partial Response

*A 58% reduction in the risk of disease progression or death was observed.

** The overall concordance rate between the investigator and IRC was 70%.

*** A high crossover rate was observed, with 82% of patients in the chemotherapy arm later receiving treatment with an EGFR tyrosine kinase inhibitor, and all but 2 of these patients later using erlotinib.

First-line chemotherapy followed by maintenance therapy for NSCLC (monotherapy with erlotinib)

The efficacy and safety of erlotinib as maintenance therapy after first-line chemotherapy for NSCLC were investigated in a randomized, double blind, placebo-controlled trial (BO18192, SATURN). This study was conducted in 889 patients with locally advanced or metastatic NSCLC who had not shown progression after four cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive either erlotinib 150 mg orally once daily or placebo until disease progression. The primary endpoint of the study was progression-free survival (PFS) for all patients. The basic demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS >1 or significant hepatic or renal comorbidities were excluded from the study.

In this study, benefit was observed in the overall population for both the primary PFS endpoint (HR=0.71, p<0.0001) and the secondary overall survival (OS) endpoint (HR=0.81, p=0.0088).

However, the greatest benefit was observed in a predefined exploratory analysis in patients with EGFR-activating mutations (n=49), showing a significant PFS benefit (HR=0.10, 95% CI, 0.04 - 0.25; p<0.0001) and an OS HR of 0.83 (95% CI, 0.34 - 2.02). In the EGFR mutation-positive subgroup, 67% of placebo patients later received second or subsequent line treatment with EGFR-TKIs.

The BO25460 (IUNO) study was conducted in 643 patients with advanced-stage NSCLC who did not have tumors with an EGFR-activating mutation (exon 19 deletion or exon 21 L858R mutation) and did not show disease progression after 4 cycles of platinum-based chemotherapy.

The aim of the study is to compare the overall survival (OS) of first-line maintenance therapy with erlotinib to erlotinib used during disease progression. The study did not meet the primary endpoint. In patients whose tumors did not have an EGFR-activating mutation, first-line maintenance therapy with erlotinib was not superior to second-line therapy with erlotinib (HR=1.02, 95% CI, 0.85 – 1.22, p=0.82). The secondary endpoint of progression-free survival (PFS) showed no difference between erlotinib and placebo in maintenance therapy (HR=0.94, 95% CI, 0.80 - 1.11; p=0.48).

According to data from the BO25460 (IUNO) study, the use of erlotinib for first-line maintenance therapy is not recommended for patients without an EGFR-activating mutation.

Treatment for NSCLC after at least one failed chemotherapy (monotherapy with erlotinib)

The efficacy and safety of erlotinib as second- and third-line treatment have been demonstrated in a randomized, double blind, placebo-controlled study (BR.21). This study included 731 patients with locally advanced or metastatic NSCLC who had received at least one chemotherapy regimen. Patients were randomized 2:1 to receive either 150 mg of oral erlotinib once daily or placebo. The study endpoints were: overall survival (OS), progression-free survival (PFS), response rate, duration of response, time to worsening of lung cancer-related symptoms (cough, dyspnea, and pain), and safety. The primary endpoint was survival.

Demographic characteristics were balanced between the two treatment groups. Two-thirds of patients were male, and approximately one-third had an ECOG performance status (PS) of 2 at baseline, with 9% having an ECOG PS of 3. Of the patients in the erlotinib and placebo groups, 93% and 92%, respectively, had previously received a platinum-based regimen, and 36% and 37%, respectively, had received taxane therapy.

In the erlotinib group, the adjusted hazard ratio (HR) for death compared to placebo was 0.73 (95% CI, 0.6 - 0.87) (p=0.001). The proportion of patients alive at 12 months was 31.2% in the erlotinib group and 21.5% in the placebo group. The median overall survival was 6.7 months (95% CI, 5.5 - 7.8 months) in the erlotinib group, compared to 4.7 months (95% CI, 4.1 - 6.3 months) in the placebo group.

The effect of erlotinib on overall survival (OS) has been examined in different patient subgroups. The impact of erlotinib on OS is similar in the following subgroups: patients with an initial performance status (ECOG) of 2-3 (HR = 0.77, 95% CI, 0.6-1) or 0-1 (HR = 0.73, 95% CI, 0.6-0.9), male patients (HR = 0.76, 95% CI, 0.6-0.9) or female patients (HR = 0.8, 95% CI, 0.6-1.1), patients under 65 years (HR = 0.75, 95% CI, 0.6-0.9) or older patients (HR = 0.79, 95% CI, 0.6-1), patients who have previously received one regimen (HR = 0.76, 95% CI, 0.6-1) or more than one regimen (HR = 0.75, 95% CI, 0.6-1), white patients (HR = 0.79, 95% CI, 0.6-1) or Asian patients (HR = 0.61, 95% CI, 0.4-1), patients with adenocarcinoma (HR = 0.71, 95% CI, 0.6-0.9) or squamous cell carcinoma (HR = 0.67, 95% CI, 0.5-0.9). The effect of erlotinib is not similar in the following subgroups: patients with other histologies (HR = 1.04,

95% CI, 0.7-1.5), patients with stage IV disease at diagnosis (HR = 0.92, 95% CI, 0.7-1.2) or patients with disease stage <IV at diagnosis (HR = 0.65, 95% CI, 0.5-0.8). Patients who have never smoked benefit more from erlotinib compared to those who currently or previously smoked (HR = 0.87, 95% CI, 0.71-1.05), showing a survival HR = 0.42, 95% CI, 0.28-0.64.

In approximately 45% of patients with known EGFR expression status, the hazard ratio for patients with EGFR-positive tumors was 0.68 (95% CI, 0.49-0.94) and for patients with EGFR-negative tumors, it was 0.93 (95% CI, 0.63-1.36) (EGFR was determined by the EGFR pharmDx kit using IHC, with tumors defined as EGFR-negative if less than 10% of tumor cells were stained). In the remaining 55% of patients with unknown EGFR expression status, the HR was 0.77 (95% CI, 0.61-0.98).

The average PFS in the erlotinib group was 9.7 weeks (95% CI, 8.4 - 12.4 weeks), and in the placebo group, it was 8 weeks (95% CI, 7.9 – 8.1 weeks).

The objective response rate according to the Response Evaluation Criteria in Solid Tumors (RECIST) was 8.9% in the erlotinib group (95% CI, 6.4 - 12). The first 330 patients were centrally evaluated (response rate 6.2%), and 401 patients were evaluated by investigators (response rate 11.2%).

The median duration of response was 34.3 weeks, ranging from 9.7 to 57.6+ weeks. The proportion of patients with a complete response, partial response, or stable disease was 44% in the erlotinib group and 27.5% in the placebo group (p = 0.004).

Survival benefit of erlotinib was also seen in patients who did not achieve an objective tumor response (according to RECIST). This was evidenced by the HR for death being 0.82 (95% CI, 0.68 – 0.99) among patients with the best response of stable disease or progressive disease.

Erlotinib showed a benefit over placebo in terms of symptoms, with a significantly longer time to worsening of cough, dyspnea, and pain.

In a double-blind, randomized Phase III study (MO22162, CURRENTS) comparing two doses of erlotinib (300 mg vs. 150 mg) in locally advanced or metastatic, smoking (average 38 pack-years) NSCLC patients after chemotherapy, the 300 mg dose did not show a progression-free survival benefit (7 weeks vs. 6.86 weeks).

All secondary endpoints are consistent with the primary endpoints, and no survival difference was observed between patients treated with 300 mg and 150 mg of erlotinib (HR 1.03, 95% CI 0.8 – 1.32). Safety data can be compared between the 300 mg and 150 mg doses, but a numerical increase in the incidence of rash, interstitial lung disease, and diarrhea was observed in patients receiving the higher dose of erlotinib. Data from the CURRENTS study showed no benefit with the 300 mg dose compared to the recommended 150 mg dose in smokers.

Patients in this study were not selected based on EGFR mutation status (see sections 4.2, 4.4, 4.5, and 5.2).

5.2 Pharmacokinetic properties

General Characteristics

Absorption:

After oral administration, erlotinib reaches peak plasma levels approximately 4 hours after the oral dose. A bioavailability of about 59% was achieved in a study conducted with normal healthy volunteers. Bioavailability after an oral dose can be increased when taken with food.

Distribution:

Erlotinib has an average apparent volume of distribution of 232 L and distributes to human tumor tissues. In a study with 4 patients (3 with non-small cell lung cancer (NSCLC) and 1 with laryngeal cancer) receiving a daily oral dose of 150 mg of erlotinib, tumor samples obtained from surgical excisions on day 9 of treatment revealed an average erlotinib concentration of 1,185 ng/g tissue. This corresponds to 63% of the average observed peak plasma concentrations in steady state (range: 5-161). Primary active metabolites were detected at average concentrations of 160 ng/g tissue, which corresponds to 113% of the overall average of the observed peak plasma concentrations in steady state (range: 88-130). Plasma protein binding is approximately 95%. Erlotinib binds to serum albumin and alpha-1 acid glycoprotein (AAG).

Biotransformation:
Erlotinib is primarily metabolized in the liver by hepatic cytochrome enzymes, mainly CYP3A4 and to a lesser extent by CYP1A2. The extrahepatic metabolism of erlotinib by CYP4A4 in the intestine, CYP1A1 in the lungs, and CYP1B1 in tumor tissue potentially contributes to the metabolic clearance of erlotinib.

Three main metabolic pathways have been identified: 1) O-demethylation of one or both side chains, followed by oxidation to the carboxylic acid; 2) oxidation of the acetylene part, followed by hydrolysis to aryl carboxylic acid; and 3) aromatic hydroxylation of the phenyl-acetylene part. The primary metabolites OSI 420 and OSI 413 formed by O-demethylation of one of the side chains have comparable effects to erlotinib in preclinical in vitro studies and in vivo tumor models. These metabolites are present in plasma at less than 10% of the amount of erlotinib and exhibit similar pharmacokinetics.

Elimination:
Erlotinib is primarily excreted as metabolites, mainly through feces (>90%), while renal elimination accounts for only a small fraction of an oral dose (approximately 9%). A population pharmacokinetic analysis in 591 patients treated with erlotinib alone revealed an average half-life of 36.2 hours and an average apparent clearance of 4.47 L/hour. Therefore, it is expected that steady-state plasma concentrations will be reached within approximately 7-8 days.

Linearity/Non-linearity:
There is insufficient data.

Patient Characteristics
No significant relationship was observed between expected apparent clearance and patient age, body weight, sex, or ethnic characteristics. Patient factors that influence erlotinib pharmacokinetics include serum total bilirubin, albumin, and alpha-1 acid glycoprotein concentrations, as well as continued smoking. Increased serum total bilirubin concentrations, as well as albumin and alpha-1 acid glycoprotein concentrations, were associated with slower erlotinib clearance. The clinical relevance of these differences is unclear. However, faster erlotinib clearance was observed in smokers. This was confirmed in a pharmacokinetic study conducted on healthy individuals, both non-smokers and current smokers, who received a single oral dose of 150 mg of erlotinib. The geometric mean of C_{max} was 1,056 ng/mL in non-smokers and 689 ng/mL in smokers, with the average ratio for smokers compared to non-smokers being 65.2% (95% CI: 44.3 to 95.9, p=0.031). The geometric mean for $AUC_{0\text{-}inf}$ was 18,726 ngh/mL in non-smokers and 6,718 ngh/mL in smokers, with the average ratio being 35.9% (95% CI: 23.7 to 54.3, p<0.0001). The geometric mean for C24h was 288 ng/mL in non-smokers and 34.8 ng/mL in smokers, with the average ratio being 12.1% (95% CI: 4.82 to 30.2, p=0.0001).

In the pivotal phase III NSCLC study, the steady-state plasma concentration of erlotinib in current smokers was 0.65 mcg/mL (n=16), which is less than half of the concentration observed in those who had quit smoking or never smoked (1.28 mcg/mL, n=108). This effect was accompanied by a 24% increase in plasma clearance of erlotinib. In a phase I dose escalation study conducted in former smokers with NSCLC, pharmacokinetic analyses showed that increasing the erlotinib dose from 150 mg to the maximum tolerated dose of 300 mg resulted in a dose-proportional increase in erlotinib exposure. In this study, the steady-state plasma concentration in current smokers treated with the 300 mg dose was 1.22 mcg/mL (n=17) (see sections 4.2, 4.4, 4.5, and 5.1).

Based on the pharmacokinetic study results, it is recommended that patients who are current smokers discontinue smoking while undergoing treatment with TARSINIB, as smoking may reduce plasma concentrations.

According to the results of the population pharmacokinetic analysis, the presence of an opioid was found to increase exposure by 11%.

Pediatric Population:
No specific studies are available for pediatric patients.

Geriatric Population:
There are no specific studies available for elderly patients.

Liver Insufficiency:
Erlotinib is primarily metabolized by the liver. In patients with solid tumors and moderate hepatic dysfunction (Child-Pugh score 7-9), the geometric means of $AUC_{0\text{-}t}$ and C_{max} for erlotinib were 27,000 ngh/mL and 805 ng/mL, respectively. These values were 29,300 ngh/mL and 1,090 ng/mL in patients with adequate hepatic function, including those with primary liver cancer or hepatic metastases. Although the C_{max} value was significantly lower in patients with moderate hepatic dysfunction, this difference is not considered clinically meaningful. There is no data available regarding the effect of severe hepatic dysfunction on erlotinib pharmacokinetics. The population pharmacokinetic analysis showed that increased serum total bilirubin concentrations were associated with a slower erlotinib clearance rate.

Renal Insufficiency:
The renal elimination of erlotinib and its metabolites is not significant. Less than 9% of a single dose is excreted in the urine. In the population pharmacokinetic analysis, no clinically meaningful relationship was observed between erlotinib clearance and creatinine clearance, but no data are available for patients with creatinine clearance less than 15 mL/min.

5.3 Preclinical safety data

Effects observed in at least one animal species or study related to chronic dosing included impacts on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, erythema, and alopecia), ovaries (atrophy), liver (hepatic necrosis), kidneys (renal papillary necrosis and tubular dilation), and the gastrointestinal system (delayed gastric emptying and diarrhea). Red blood cell parameters were decreased, and white blood cells, primarily neutrophils, were increased. Alanine aminotransferase (ALT), aspartate aminotransferase

(AST), and bilirubin levels increased in association with treatment. These findings occurred at exposures below clinically meaningful levels. Based on the mechanism of action, erlotinib has the potential to be teratogenic. Reproductive toxicology studies in rats and mice, conducted at the maximum tolerated dose and/or maternally toxic doses, showed reproductive (embryotoxicity in rats, embryo resorption, and fetotoxicity in rabbits) and developmental (reduced pup growth and survival in rats) toxicity; however, these effects were not teratogenic and did not negatively impact fertility. These findings occurred at all clinically relevant exposure levels.

Conventional genotoxicity studies showed negative results for erlotinib. Two-year carcinogenicity studies in rats and mice with erlotinib showed negative results at exposures exceeding human therapeutic levels (based on C_{max} and/or AUC, up to 2 times and 10 times higher, respectively).

In rats, mild phototoxic skin reactions were observed after UV irradiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate (pharmatose 200 M) (from cow's milk)
Microcrystalline cellulose (avicel pH 102)
Sodium starch glycolate (primogel)
Sodium lauryl sulfate (SLS)
Colloidal silicon dioxide (aerosil 200)
Magnesium stearate

Opadry White OY 58900:
HPMC 2910 / hypromellose
Titanium dioxide
Macrogol / PEG

6.2 Incompatibilities

There is insufficient data.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 30°C, protected from moisture.

6.5 Nature and contents of container

Packaged in transparent PVC/Aclar and aluminum foil blister packs. Blisters are packed in cardboard boxes. Each cardboard box contains blisters with 30 tablets and a package leaflet.

6.6 Special precautions for disposal and other handling

Disposal of unused/expired products:
Pharmaceutical products should not be disposed of in the environment. Medicines should not be disposed of via wastewater or household waste. If available, equipped waste collection systems in the local area should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

2017/692

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 15.09.2017
Date of latest renewal :

10. DATE OF REVISION OF THE SPC