SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TARSINIB 100 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each film-coated tablet contains 109.28 mg erlotinib hydrochloride equivalent to 100 mg erlotinib.

Excipient(s):
Lactose monohydrate (derived from cow's milk) 70.85 mg
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film Coated Tablets
White, round, biconvex film tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer:
TARSINIB is indicated for the first-line treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC) whose epidermal growth factor receptor (EGFR) gene exon 19 deletion and/or exon 21 (L858R) mutation detected by an accredited laboratory test, and for use as second-line therapy up to progression after progression of first-line chemotherapy in patients with non-squamous non-small cell lung cancer with deletion.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
Treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

Unless recommended otherwise by the doctor;
Standard dose:
Non-small cell lung cancer:
In patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have not received first-line chemotherapy, EGFR mutation testing should be performed before initiating TARSINIB therapy.

The recommended daily dose of TARSINIB is 150 mg taken at least one hour before or two hours after the ingestion of food. It can be used at a maximum daily dose of 150 mg.

Method of administration:
Taken by mouth.

Additional information on special populations:
Concomitant use of CYP3A4 substrates and modulators may require dose adjustment (see section 4.5).

When dose adjustment is necessary, the dose should be reduced in 50 mg steps (see sections 4.4 and 4.5).

Hepatic insufficiency:
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 TARSINIB to patients with hepatic impairment. Dose reduction or interruption of TARSINIB should be considered if severe adverse reactions occur. The safety and efficacy of erlotinib has not been studied in patients with severe hepatic dysfunction (see sections 4.4 and 5.2). TARSINIB should not be used in patients with total bilirubin 3 times greater than the upper limit of normal.

Asymptomatic elevations in liver transaminases have been observed in patients treated with erlotinib. Therefore, liver function tests should be monitored when administering TARSINIB to patients with hepatic dysfunction.

TARSINIB treatment should be interrupted or discontinued in the following situations;

TARSINIB therapy should be interrupted or discontinued if pre-treatment values are outside of the normal range or if changes in liver function occur, such as doubling of total bilirubin and/or tripling of transaminases.

In case of undesirable changes in liver function tests, dose reduction should be considered, provided that treatment is interrupted and/or followed by frequent liver function tests before worsening of laboratory findings.

In patients with normal pre-treatment values, TARSINIB therapy should be interrupted or discontinued if total bilirubin is greater than 3 times the upper limit of normal and/or transaminases are greater than 5 times the upper limit of normal (see sections 4.4, 4.8 and 5.2.).

Rare cases of hepatic failure (some of which may be fatal) have been reported during post-marketing use of erlotinib. Therefore, periodic liver function tests (transaminases, bilirubin and alkaline phosphatase) are recommended. If changes in liver function are severe, TARSINIB should be discontinued (see section 4.8).

Dose reduction in moderate hepatic impairment and discontinuation of treatment in severe hepatic impairment are required. When dose adjustment is required, it is recommended to reduce the dose in 50 mg steps.

Renal insufficiency:
The safety and efficacy of erlotinib has not been studied in patients with renal impairment (serum creatinine concentration >1.5 times the upper normal limit) (see section 5.2).

Cases of acute renal failure (some of which may be fatal) with or without hypokalemia have been reported. Some were associated with concomitant chemotherapy, while others were the result of secondary dehydration due to diarrhea, vomiting and/or loss of appetite.

In the event of dehydration, especially in patients with concomitant risk factors for renal failure (e.g. pre-existing kidney disease, drug or medical conditions causing kidney disease, other pre-treatment conditions including advanced age), TARSINIB therapy should be discontinued and the patient

should be intensively rehydrated. In patients at risk for dehydration, periodic monitoring of renal function and serum electrolytes is recommended (see section 4.8).

In moderate renal impairment, the dose should be reduced, and in severe renal impairment, the dose should be discontinued. When dose adjustment is required, it is recommended to reduce the dose in 50 mg steps.

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

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

Smokers
Cigarette smoking has been shown to reduce erlotinib exposure by 50-60%. The maximum tolerated dose of TARSINIB in Non-Small Cell Lung Cancer (NSCLC) patients who currently smoke cigarettes was 300 mg. In patients who continue to smoke, the efficacy and long-term safety of a higher than recommended starting dose has not been established (see sections 4.5 and 5.2). Therefore, current smokers should be advised to stop smoking, as plasma concentrations of erlotinib in smokers as compared to non-smokers are reduced. It is recommended not to use TARSINIB together with smoking, since smoking reduces the effectiveness of erlotinib.

4.3 Contraindications

TARSINIB is contraindicated in case of hypersensitivity to erlotinib or any of the excipients.

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status:
When assessing a patient's EGFR mutation status, it is important to choose a validated and robust method to avoid false positive or false negative results.

Smokers:
Because of the lower plasma concentrations of erlotinib in smokers compared to non-smokers, current smokers should be advised to quit smoking. The degree of decrease in concentration is expected to be clinically relevant (see section 4.5). It is recommended not to use erlotinib with smoking, since smoking reduces the effectiveness of erlotinib.

Interstitial Lung Disease:
Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib for treatment of non-small cell lung cancer (NSCLC). In the pivotal randomized placebo-controlled phase III study BR.21 in NSCLC, the incidence of severe ILD-like events was 0.8% in both placebo and erlotinib groups. In a meta-analysis of NSCLC randomized controlled clinical trials (excluding phase I and single-arm phase II studies due to lack of control groups), the incidence of ILD-like events was 0.9% on erlotinib compared to 0.4% in patients in the control arms. 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), lung infiltration, and alveolitis. 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. A higher incidence of ILD (approximately 5% with a mortality rate of 1.5%) is seen among patients in studies conducted in Japan.

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnea, cough and fever, TARSINIB therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARSINIB should be discontinued and appropriate treatment initiated as necessary (see section 4.8).

Diarrhea, dehydration, electrolyte imbalance and renal failure:
Diarrhea (including very rare cases with a fatal outcome) has occurred in approximately 50% of patients on erlotinib and moderate or severe diarrhea should be treated with e.g. loperamide. In some cases, dose reduction may be necessary. In the clinical studies, doses were reduced by 50 mg steps. Dose reductions by 25 mg steps have not been investigated. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, TARSINIB therapy should be interrupted and appropriate measures should be taken to treat the dehydration (see section 4.8). There have been rare reports of hypokalemia and renal failure (including fatalities). Some cases were secondary to severe dehydration due to diarrhea, vomiting and/or anorexia, while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (especially concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), TARSINIB 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:
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 4.8). Erlotinib is not recommended for use in patients with severe hepatic dysfunction.

Gastrointestinal perforation:
Patients receiving TARSINIB 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. TARSINIB should be 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). TARSINIB treatment should be interrupted or discontinued if the patient develops bullous, blistering or exfoliating conditions. Patients with bullous and exfoliative skin disorders should be tested for skin infection and treated according to local management guidelines.

Ocular disorders:
Rare cases of severe keratitis and ulcerative keratitis have been reported post-marketing surveillance. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred

promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with 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. Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib (see section 4.8).

Interactions with other medicinal products:
Potent inducers of CYP3A4 may reduce the efficacy of erlotinib whereas potent inhibitors of CYP3A4 may lead to increased toxicity. Concomitant treatment with these types of agents should be avoided (see section 4.5).

Other forms of interactions:
Erlotinib is characterized by a decrease in solubility at pH above 5. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of TARSINIB when co-administered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H_2 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 is considered necessary during treatment with TARSINIB, they should be taken at least 4 hours before or 2 hours after the daily dose of TARSINIB.

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

Excipients:
TARSINIB contains lactose monohydrate. Therefore, patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Erlotinib and other CYP substrates:
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.

When erlotinib was co-administered with ciprofloxacin, a moderate CYP1A2 inhibitor, the erlotinib exposure [AUC] increased significantly by 39%, while no statistically significant change in Cmax was found. Similarly, the exposure to the active metabolite increased by about 60% and 48% for AUC and Cmax, 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 erlotinib. If adverse reactions related to erlotinib are observed, the dose of erlotinib may be reduced.

Pre-treatment or co-administration of erlotinib 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 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 metabolized 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 tumor tissue also potentially contribute to the metabolic clearance of erlotinib. Potential interactions may occur with active substances, which are metabolized by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg orally twice daily for 5 days) resulted in an intense erlotinib exposure (86% increase in median erlotinib exposure [AUC - area under the curve]) and an 69% increase in Cmax 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, and voriconazole), protease inhibitors, erythromycin or clarithromycin. If necessary, the dose of erlotinib should be reduced, particularly if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib 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 erlotinib resulted in a mean erlotinib exposure (AUC) of 57.5% of that after a single 150 mg erlotinib dose in the absence of rifampicin treatment. Co-administration of erlotinib with CYP3A4 inducers should therefore be avoided. 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 (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. 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 erlotinib. Alternate treatments lacking potent CYP3A4 inducing activity should be considered when possible.

Erlotinib and coumarin-derived anticoagulants:
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.

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

Erlotinib and smokers:
Results of a pharmacokinetic interaction study indicated a significant 2.8-, 1.5- and 9-fold reduced AUCinf, Cmax and plasma concentration at 24 hours, respectively, after administration of erlotinib 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 erlotinib, as plasma erlotinib concentrations are reduced otherwise. The clinical effect of reduced exposure has not been formally investigated, but it is thought that reduced exposure may be clinically significant.

Erlotinib and P-glycoprotein inhibitors:
Erlotinib is a substrate for the P-glycoprotein active substance transporter. Concomitant administration of inhibitors of Pgp, (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 have not been established. Caution should be exercised in such situations.

Erlotinib and medicinal products altering pH:
Erlotinib is characterized by a decrease in solubility at pH above 5. Medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor (PPI), decreased the erlotinib exposure [AUC] and maximum concentration [Cmax] by 46% and 61%, respectively. There was no change to Tmax or half-life. Concomitant administration of erlotinib with 300 mg ranitidine, an H2-receptor antagonist, decreased erlotinib exposure [AUC] and maximum concentrations [Cmax] by 33% and 54%, respectively. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. However, when erlotinib 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 [Cmax] decreased only by 15% and 17%, respectively. The effect of antacids on the absorption of erlotinib has not been investigated but absorption may be impaired, leading to lower plasma levels. In summary, the combination of erlotinib with proton pump inhibitors should be avoided. If the use of antacids is considered necessary during treatment with erlotinib, they should be taken at least 4 hours before or 2 hours after the daily dose of erlotinib. If the use of ranitidine is considered, it should be used in a staggered manner; erlotinib must be taken at least 2 hours before or 10 hours after ranitidine dosing.

Erlotinib and Gemcitabine:
In a Phase Ib study, 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 and Carboplatin/Paclitaxel interaction:
Erlotinib increases platinum concentrations. In a clinical study, the concomitant use of erlotinib with carboplatin and paclitaxel led to an increase of total platinum AUC0-48 of 10.6%. Although statistically significant, the magnitude of this difference is not considered 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.

Erlotinib and Capecitabine:
Capecitabine may increase erlotinib concentrations. When erlotinib was given in combination with capecitabine, there was a statistically significant increase in erlotinib AUC and a borderline increase in Cmax when compared with values observed in another study in which erlotinib was given as single agent. There were no significant effects of erlotinib on the pharmacokinetics of capecitabine.

Erlotinib and proteasome inhibitors:
Due to the working mechanism, proteasome inhibitors including bortezomib may be expected to influence the effect of EGFR inhibitors including erlotinib. Such influence is supported by limited clinical data and preclinical studies showing EGFR degradation through the proteasome.

Additional information on special populations:
No interaction studies have been conducted in special populations.

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

4.6. Fertility, pregnancy and lactation

General recommendation
Pregnancy category: D

Women of childbearing potential/Contraception
Women of childbearing potential must be advised to avoid becoming pregnant while taking TARSINIB. Adequate contraceptive methods should be used during treatment and for a further two weeks after completion of treatment.

Pregnancy
There are no adequate data for the use of erlotinib in pregnant women. 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/fetal lethality (see section 5.3). The potential risk for humans is unknown. TARSINIB should not be used during pregnancy unless necessary. Treatment in pregnant women should only be continued if the expected benefits to the mother clearly outweigh the risks to the fetus.

Breast-feeding
It is not known whether erlotinib is excreted in human milk. Considering the potential for harm to the infant, mothers should be warned not to breastfeed while receiving TARSINIB.

Reproduction ability / 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 (see section 5.3). 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; however, erlotinib is not associated with impairment of mental ability.

4.8. Undesirable effects

Non-Small Cell Lung Cancer (NSCLC)
(erlotinib administered as monotherapy)

In a randomized double-blind study (BR.21; erlotinib administered as second line therapy), rash (75%) and diarrhea (54%) were the most commonly reported adverse drug reactions (ADRs). Most were grade 1 or grade 2 in severity and manageable without intervention. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively in erlotinib-treated patients and each resulted in study

discontinuation in 1% of patients. Dose reduction for rash and diarrhea was needed in 6% and 1% of patients, respectively. In study BR.21, the median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

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.

In the pivotal study BR.21; adverse reactions that occurred more frequently (≥3%) in erlotinib-treated patients than in the placebo group and in at least 10% of patients in the erlotinib group are summarized by National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade in Table 1.

The following terms are used to sort undesirable effects according to their frequency: 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); unknown (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Very common (at least 10% of patients) ADRs observed in the BR.21 baseline study

	Erlotinib n=485			Placebo n=242		
NCI-CTC Grade	Any Grade	3	4	Any Grade	3	4
MedDRA Preferred Term	%	%	%	%	%	%
Total patients with any adverse events	99	40	22	96	36	22
Infections and infestations						
Infection*	24	4	0	15	2	0
Metabolism and nutrition disorders						
Anorexia	52	8	1	38	5	<1
Eye disorders						
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Gastrointestinal disorders						
Diarrhea**	54	6	<1	18	<1	0
Nausea	33	3	0	24	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1
Skin and subcutaneous tissue disorders						
Rash***	75	8	<1	17	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
General disorders and administration site conditions						
Fatigue	52	14	4	45	16	4

* Severe infections, with or without neutropenia, have included pneumonia, sepsis, and cellulitis.
** Can lead to dehydration, hypokalemia and renal failure.
*** Rash included dermatitis acneiform.

In two other double-blind, randomized, placebo-controlled Phase III studies BO18192 (SATURN) and BO25460 (IUNO); erlotinib was administered as maintenance after first-line chemotherapy. These studies were conducted in a total of 1532 patients with advanced, recurrent or metastatic NSCLC following first-line standard platinum-based chemotherapy. No new safety signals were identified.

The most frequent ADRs seen in erlotinib-treated patients in studies BO18192 and BO25460 were rash and diarrhea (see Table 2). No Grade 4 rash or diarrhea was observed in either study. Rash and diarrhea resulted in discontinuation of erlotinib in 1% and <1% of patients, respectively, in study BO18192, while no patients discontinued for rash or diarrhea in BO25460. Dose modifications (interruptions or reductions) for rash and diarrhea were needed in 8.3% and 3% of patients, respectively, in study BO18192 and 5.6% and 2.8% of patients, respectively, in study BO25460.

Table 2: Most frequent ADRs in studies BO18192 (SATURN) and BO25460 (IUNO)

	BO18192 (SATURN)*		**BO25460 (IUNO)***	
	Erlotinib n=433	**Placebo n=445**	**Erlotinib n=322**	**Placebo n=319**
	%	**%**	**%**	**%**
Rash, any grades	49,2	5,8	39,4	10,0
Grade 3	6,0	0	5,0	1,6
Diarrhea, any grades	20,3	4,5	24,2	4,4
Grade 3	1,8	0	2,5	0,3

**Safety analysis population*

In an open-label, randomized phase III study, ML20650 conducted in 154 patients, the safety of erlotinib for first-line treatment of NSCLC patients with EGFR activating mutations was assessed in 75 patients; no new safety signals were observed in these patients.

The most frequent advers reactions seen in patients treated with erlotinib in study ML20650 were rash and diarrhea (any Grade 80% and 57%, respectively), most were Grade 1/2 in severity and manageable without intervention. Grade 3 rash and diarrhea occurred in 9% and 4% of patients, respectively. No Grade 4 rash or diarrhea was observed. Both rash and diarrhea resulted in discontinuation of erlotinib in 1% of patients. Dose modifications (interruptions or reductions) for rash and diarrhea were needed in 11% and 7% of patients, respectively.

Other observations:
Safety evaluation of erlotinib is based on the data from more than 1500 patients treated with at least one 150 mg dose of erlotinib monotherapy and more than 300 patients who received erlotinib 100 or 150 mg in combination with gemcitabine.

The following adverse reactions have been observed in patients who received single-agent erlotinib or who received erlotinib concomitantly with chemotherapy:

Very common adverse reactions are listed in Table 1; adverse reactions categorized in other frequencies are listed in Table 3.

Table 3: Summary of ADRs per frequency category:

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)

Eye disorders		- Keratitis - Conjunctivitis[1]	- Eyelash changes[2]		- Corneal perforations - Corneal ulcerations - Uveitis
Respiratory, thoracic and mediastinal disorders		- Epistaxis	- Interstitial lung disease (ILD)[3]		
Gastro-intestinal disorders	- Diyare[7]	- Gastro-intestinal kanama[4,7]	- Gastrointestinal perforasyonlar[7]		
Hepato-biliary disorders	- Liver function test abnormalities[5]			- Hepatic failure[6]	
Skin and subcutaneous tissue disorders		- Alopecia - Dry skin[1] - Paronychia - Folliculitis - Acne/Dermatitis acneiform - Skin fissures	- Hirsutism - Eyebrow changes - Brittle and loose nails - Mild skin reactions such as hyperpigmentation	- Palmar plantar erythrodysesthesia syndrome	- Stevens-Johnson syndrome/Toxic epidermal necrolysis
Renal and urinary disorders		- Renal insufficiency	- Nephritis - Proteinuria		

[1] In clinical study PA.3.
[2] Including in-growing eyelashes, excessive growth and thickening of the eyelashes.
[3] Including fatalities, in patients receiving TARSINIB for treatment of NSCLC or other advanced solid tumors. A higher incidence has been observed in patients in Japan (see section 4.4).
[4] In clinical studies, some cases have been associated with concomitant warfarin administration and some with concomitant NSAID administration (see section 4.5).
[5] Including increased alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin. These were very common in clinical study PA.3 and common in clinical study BR.21. 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).

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 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 reactions such as diarrhea, rash and possibly increased activity of liver aminotransferases may occur above the recommended dose.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, protein kinase inhibitor
ATC code: L01EB02

Mechanism of Action:
Erlotinib is an epidermal growth factor receptor/human epidermal growth factor receptor type 1 (EGFR also known asHER1) tyrosine kinase inhibitor. Erlotinib potently inhibits the intracellular phosphorylation of EGFR. EGFR/HER1 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.

EGFR mutations may lead to constitutive activation of anti-apoptotic and proliferation signaling pathways. The potent effectiveness of erlotinib in blocking EGFR-mediated signaling in these EGFR mutation positive tumors 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. Tumor regression is observed in mouse models of enforced expression of these EGFR activating mutations.

Efficacy/Clinical Studies:

Clinical efficacy
- First-line Non-Small Cell Lung Cancer (NSCLC) therapy for patients with EGFR activating mutations (erlotinib administered as monotherapy):
The efficacy of erlotinib in first-line treatment of patients with EGFR activating mutations in NSCLC was demonstrated in a phase III, randomized, open-label trial (ML20650, EURTAC). This study was conducted in Caucasian patients with metastatic or locally advanced NSCLC (stage IIIB and IV) who have not received previous chemotherapy or any systemic antitumor therapy for their advanced disease and who present mutations in the tyrosine kinase domain of the EGFR (exon 19 deletion or exon 21 mutation). Patients were randomized 1:1 to receive erlotinib 150 mg daily or up to 4 cycles of platinum-based doublet chemotherapy.

The primary endpoint was investigator assessed progression free survival (PFS), the efficacy results are summarized in Table 4.

Figure 1: Kaplan-Meier curve for investigator assessed PFS in trial ML20650 (EURTAC) (April 2012 cut-off)

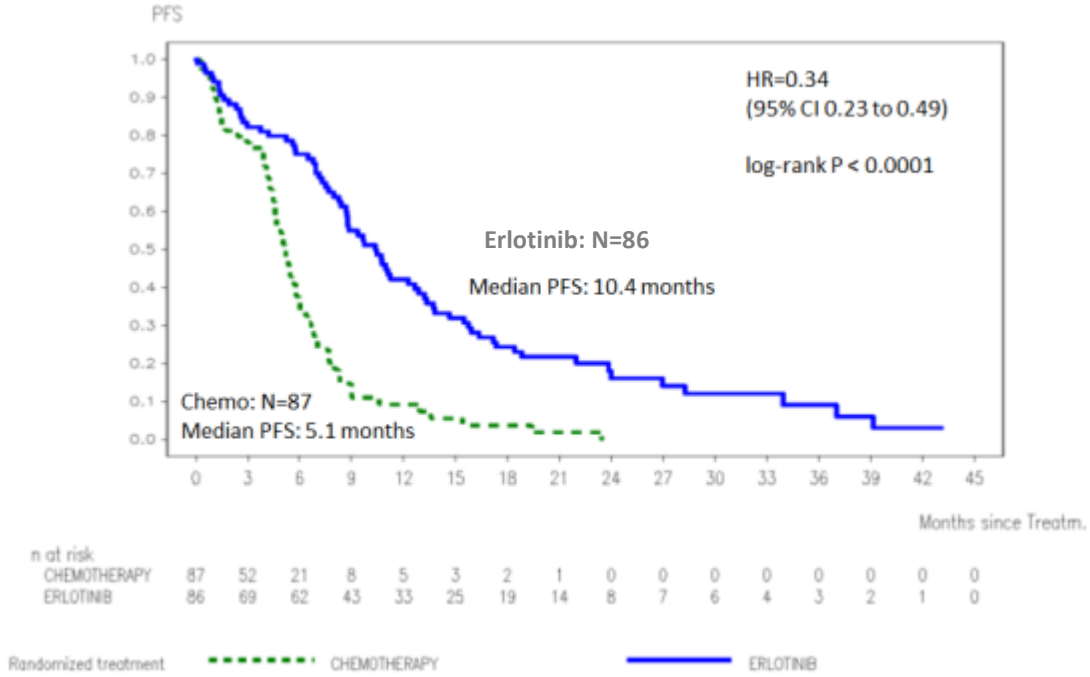

Table 4: Efficacy results of erlotinib versus chemotherapy in trial ML20650 (EURTAC)

		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 ** Independent Review **	9.4 10.4	5.2 5.4	0.42 [0.27-0.64] 0.47 [0.27-0.78]	p<0.0001 p=0.003
	Best Overall Response Rate (CR/PR)	54.5%	10.5%		p<0.0001
	Overall Survival (OS) (months)	22.9	18.8	0.80 [0.47-1.37]	p=0.4170
Exploratory 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.
** Overall concordance rate between investigator and IRC assessment was 70%.
*** A high crossover was observed with 82% of the patients in the chemotherapy arm receiving subsequent therapy with an EGFR tyrosine kinase inhibitor and all but 2 of those patients had subsequent erlotinib.

- Maintenance NSCLC therapy after first-line chemotherapy (erlotinib administered as monotherapy):

The efficacy and safety of erlotinib as maintenance after first-line chemotherapy for NSCLC was 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 did not progress after 4 cycles of platinum-based doublet chemotherapy. Patients were randomized 1:1 to receive erlotinib 150 mg or placebo orally once daily until disease progression. The primary endpoint of the study included progression free survival (PFS) in all patients. Baseline demographic and disease characteristics were well balanced between the two treatment arms. Patients with ECOG PS>1, significant hepatic or renal co-morbidities were not included in the study.

In this study, the overall population showed a benefit for the primary PFS end-point (HR= 0.71 p< 0.0001) and the secondary overall survival (OS) end-point (HR= 0.81 p=0.0088). However the largest benefit was observed in a predefined exploratory analysis in patients with EGFR activating mutations (n= 49) demonstrating a substantial PFS benefit (HR=0.10, 95% CI, 0.04 to 0.25; p<0.0001) and an overall survival HR of 0.83 (95% CI, 0.34 to 2.02). 67% of placebo patients in the EGFR mutation positive subgroup received second or further line treatment with EGFR-TKIs.

- NSCLC treatment after failure of at least one prior chemotherapy regimen (erlotinib administered as monotherapy):
The efficacy and safety of erlotinib as second-third line therapy was demonstrated in a randomized, double-blind, placebo-controlled trial (BR.21), in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomized 2:1 to receive erlotinib 150 mg or placebo orally once daily. Study endpoints: overall survival, progression-free survival (PFS), response rate, duration of response, time to deterioration of lung cancer-related symptoms (cough, dyspnea and pain), and safety. The primary endpoint was survival.

Demographic characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male and approximately one-third had a baseline ECOG performance status (PS) of 2, and 9% had a baseline ECOG PS of 3. 93% and 92% of all patients in the erlotinib and placebo groups, respectively, had received a prior platinum-containing regimen and 36% and 37% of all patients, respectively, had received a prior taxane therapy.

The adjusted hazard ratio (HR) for death in the erlotinib group relative to the placebo group was 0.73 (95% CI, 0.60 to 0.87) (p = 0.001). The percent of patients alive at 12 months was 31.2% and 21.5%, for the erlotinib and placebo groups, respectively. The median overall survival was 6.7 months in the erlotinib group (95% CI, 5.5 to 7.8 months) compared with 4.7 months in the placebo group (95% CI, 4.1 to 6.3 months).

The effect on overall survival was explored across different patient subsets. The effect of erlotinib on overall survival was similar in patients with: a baseline performance status (ECOG) of 2-3 (HR = 0.77, 95% CI 0.6-1.0) or 0-1 (HR = 0.73,95% CI 0.6-0.9), male (HR = 0.76, 95% CI 0.6-0.9) or female patients (HR = 0.80, 95% CI 0.6-1.1), patients < 65 years of age (HR = 0.75, 95% CI 0.6-0.9) or older patients (HR = 0.79, 95% CI 0.6-1.0), patients with one prior regimen (HR =0.76, 95% CI

0.6-1.0) or more than one prior regimen (HR = 0.75, 95% CI 0.6-1.0), Caucasian (HR = 0.79, 95% CI 0.6-1.0) or Asian patients (HR = 0.61, 95% CI 0.4-1.0), 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). But not in 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 stage <IV disease at diagnosis (HR =0.65, 95% CI 0.5-0.8). Patients who never smoked had a much greater benefit from erlotinib (survival HR = 0.42, 95% CI0.28-0.64) compared with current or ex-smokers (HR = 0.87, 95% CI 0.71-1.05).

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

The median PFS was 9.7 weeks in the erlotinib group (95% CI, 8.4 to 12.4 weeks) compared with 8.0 weeks in the placebo group (95% CI, 7.9 to 8.1 weeks).

The objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) in the erlotinib group was 8.9% (95% CI, 6.4 to 12.0). The first 330 patients were centrally assessed (response rate 6.2%); 401 patients were investigator-assessed (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 who experienced complete response, partial response or stable disease was 44.0% and 27.5%, respectively, for the erlotinib and placebo groups (p = 0.004).

A survival benefit of erlotinib was also observed in patients who did not achieve an objective tumor response (by RECIST). This was evidenced by a HR for death of 0.82 (95% CI, 0.68 to 0.99) among patients, whose best response was stable disease or progressive disease.

Erlotinib resulted in symptom benefits by significantly prolonging time to deterioration in cough, dyspnea and pain, versus placebo.

5.2. Pharmacokinetic properties

General 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%. 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 tumor tissue of humans. In a study of 4 patients (3 with non-small cell lung cancer [NSCLC], and 1 with laryngeal cancer) receiving 150 mg daily oral doses of erlotinib, tumor samples from surgical excisions on Day 9 of treatment revealed tumor concentrations of erlotinib that averaged 1185 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 tumor at concentration save raging 160 ng/g tissue, which corresponded to an overall average of 113% (range 88-130%) of the observed steady state peak plasma concentrations. Plasma protein binding is approximately 95%. Erlotinib binds to serum albumin andalpha-1 acid glycoprotein (AAG).

Biotransformation:
Erlotinib is metabolized 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 tumor tissue potentially contribute to the metabolic clearance of erlotinib.

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* tumor 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 faces (>90%) with renal elimination accounting for only a small amount (approximately 9%) of an oral dose. A population pharmacokinetic analysis in 591 patients receiving single agent 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.

Linearity/Non-linearity:
No adequate data.

Characteristic features in patients
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, concentrations of albumin and alpha-1 acid glycoprotein and current smoking. Increased serum concentrations of total bilirubin and concentrations of albumin and alpha-1 acid glycoprotein were associated with a reduced erlotinib clearance. The clinical relevance of these differences is unclear. However, smokers had an increased rate of erlotinib clearance. This was confirmed in a pharmacokinetic study in non-smoking and currently cigarette smoking healthy subjects receiving a single oral dose of 150 mg erlotinib. The geometric mean of the Cmax was 1056 ng/mL in the non-smokers and 689 ng/mL in the smokers with a mean ratio for smokers to non-smokers of 65.2% (95% CI: 44.3 to 95.9, p = 0.031). The geometric mean of the AUC0-inf was 18726 ng•h/mL in the non-smokers and 6718 ng•h/mL in the smokers with a mean ratio of 35.9% (95% CI: 23.7 to 54.3, p < 0.0001). The geometric mean of the C24h was 288 ng/mL in the non-smokers and 34.8 ng/mL in the smokers with a mean ratio of 12.1% (95% CI: 4.82 to 30.2, p = 0.0001).

In the pivotal Phase III NSCLC trial, current smokers achieved erlotinib steady state trough plasma concentration of 0.65 µg/mL 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 a phase I dose escalation study 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 this study was 1.22 µg/mL (n=17).
Based on population pharmacokinetic analysis, the presence of an opioid appeared to increase exposure by about 11%.

Pediatric population:
There have been no specific studies in pediatric patients.

Geriatric population:
There have been no specific studies in elderly patients.

Hepatic impairment:
Erlotinib is primarily cleared by the liver. In patients with solid tumors and with moderately impaired hepatic function (Child-Pugh score 7-9), geometric mean erlotinib AUC0-t and Cmax was 27000 ng•h/mL and 805 ng/mL, respectively, as compared to 29300 ng•h/mL and 1090 ng/mL in patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases. Although the Cmax 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. 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.

5.3. Preclinical safety data

Chronic dosing effects observed in at least one animal species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (liver necrosis), kidney (renal papillary necrosis and tubular dilatation), and gastrointestinal tract (delayed gastric emptying and diarrhea). Red blood cell parameters were decreased and white blood cells, primarily neutrophils, were increased. There were treatment-related increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. These findings were observed at exposures well below clinically relevant exposures. Based on the mode of action, erlotinib has the potential to be a teratogen. Data from reproductive toxicology tests in rats and rabbits at doses near the maximum tolerated dose and/or maternally toxic doses showed reproductive (embryotoxicity in rats, embryo resorption and fetotoxicity in rabbits) and developmental (decrease in pup growth and survival in rats) toxicity, but was not teratogenic and did not impair fertility. These findings were observed at clinically relevant exposures.

Erlotinib tested negative in conventional genotoxicity studies. Two-year carcinogenicity studies with erlotinib conducted in rats and mice were negative up to exposures exceeding human therapeutic exposure (up to 2-fold and 10-fold higher, respectively, based on Cmax and/or AUC).
A mild phototoxic skin reaction was observed in rats after UV irradiation.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (derived from cow's milk)
Microcrystalline cellulose
Sodium starch glycolate
Sodium lauryl sulfate

Colloidal silicon dioxide
Magnesium stearate
HPMC 2910/hypromellose
Titanium dioxide
Macrogol/PEG

6.2. Incompatibilities

No adequate 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

Transparent PVC/Aclar – Alu foil blister packaging. Blisters are packed in cardboard boxes. 30 tablets are presented with a package leaflet in a cardboard box.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece/ISTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER

2017/690

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 TEXT