

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40 mg film-coated tablets
TAGRISSO 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAGRISSO 40 mg tablets

Each tablet contains 40 mg osimertinib (as mesylate).

TAGRISSO 80 mg tablets

Each tablet contains 80 mg osimertinib (as mesylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

TAGRISSO 40 mg tablets

Beige, 9 mm, round, biconvex tablet, debossed with “AZ” and “40” on one side and plain on the reverse.

TAGRISSO 80 mg tablets

Beige, 7.25 x 14.5 mm, oval, biconvex tablet, debossed with “AZ” and “80” on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAGRISSO is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC).

4.2 Posology and method of administration

Treatment with TAGRISSO should be initiated by a physician experienced in the use of anticancer therapies.

When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is necessary that EGFR T790M mutation status is determined. EGFR T790M mutation status should be determined by a clinical laboratory using a validated test method (see section 4.4).

Posology

The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity.

If a dose of TAGRISSO is missed, the dose should be made up unless the next dose is due within 12 hours.

TAGRISSO can be taken with or without food at the same time each day.

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily.

Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1. TAGRISSO dose adjustment information for adverse reactions

Target organ	Adverse reaction^a	Dose modification
<i>Pulmonary</i>	ILD/Pneumonitis	Permanently discontinue TAGRISSO
<i>Cardiac</i>	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue TAGRISSO
<i>Other</i>	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO

^a Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

ECGs: Electrocardiograms; QTc: QT interval corrected for heart rate

Special populations

No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status (see section 5.2).

Hepatic impairment

No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin <upper limit of normal (ULN) and aspartate aminotransferase (AST) between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5x ULN and any AST) but caution should be used when administering TAGRISSO to these patients. The safety and efficacy of this medicinal product has not been established in patients with moderate or severe hepatic impairment. Until additional data become available, use in patients with moderate or severe hepatic impairment is not recommended (see section 5.2).

Renal impairment

No dose adjustment is recommended in patients with mild and moderate renal impairment. Limited data are available in patients with severe renal impairment. The safety and efficacy of this medicinal

product has not been established in patients with end-stage renal disease [creatinine clearance (CLcr) <15 mL/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end stage renal impairment (see section 5.2).

Paediatric population

The safety and efficacy of TAGRISSO in children or adolescents aged less than 18 years have not been established. No data are available.

Method of administration

This medicinal product is for oral use. The tablet should be swallowed whole with water and it should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50 mL of non-carbonated water. It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 15 mL for the residue rinses. The resulting 30 mL of liquid should be administered as per the naso-gastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

St. John's wort should not be used together with TAGRISSO (see section 4.5).

4.4 Special warnings and precautions for use

Assessment of EGFR T790M mutation status

When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR T790M mutation status is determined. A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Only robust, reliable and sensitive tests with demonstrated utility for the determination of T790M mutation status of tumour derived DNA (from a tissue or a plasma sample) should be used.

Positive determination of T790M mutation status using either a tissue-based or plasma-based test indicates eligibility for treatment with TAGRISSO. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

Interstitial lung disease (ILD)

Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with TAGRISSO in clinical studies. Most cases improved or resolved with interruption of treatment. Patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies (see section 4.8).

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 2.9% and were fatal in 0.3% of the 1221 patients who received TAGRISSO across clinical trials. ILD or ILD-like adverse reactions were reported in 11/411 (2.7%) of patients who received TAGRISSO in the two Phase II studies, of which 0.7% were Grade 3 or 4 and 1% were fatal. The incidence of ILD was 6.2% in patients of Japanese ethnicity, 1.2% in patients of Asian ethnicity and 2.4% in non-Asian patients. (See Section 4.8).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, TAGRISSO should be permanently discontinued and appropriate treatment initiated as necessary.

QTc interval prolongation

QTc interval prolongation occurs in patients treated with TAGRISSO. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. No arrhythmic events were reported in AURAex or AURA2 (see section 4.8). Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 ms) were excluded from these studies (see section 4.8).

When possible, the use of osimertinib in patients with congenital long QT syndrome should be avoided. Periodic monitoring with electrocardiograms (ECGs) and electrolytes should be conducted in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Treatment should be withheld in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume TAGRISSO at a reduced dose as described in Table 1. Osimertinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may increase the exposure of BCRP substrates.

Active substances that may increase osimertinib plasma concentrations

In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, co-administration with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib (area under the curve (AUC) increased by 24% and C_{max} decreased by 20%). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib. Further catalyzing enzymes have not been identified.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced by 78% when co-administered with rifampicin (600 mg daily for 21 days). Similarly, the exposure to metabolite, AZ5104 decreased by 82% for the AUC and 78% for C_{max} . It is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with TAGRISSO should be avoided. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil) may also decrease osimertinib exposure and should be used with caution, or avoided when

possible. There are no clinical data available to recommend a dose adjustment of TAGRISSO. Concomitant use of St. John's Wort is contraindicated (see section 4.3).

Effect of gastric acid reducing active substances on osimertinib

In a clinical pharmacokinetic study, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures. Gastric pH modifying agents can be concomitantly used with TAGRISSO without any restrictions.

Active substances whose plasma concentrations may be altered by TAGRISSO

Based on *in vitro* studies, osimertinib is a competitive inhibitor of BCRP transporters.

In a clinical PK study, co-administration of TAGRISSO with rosuvastatin (sensitive BCRP substrate) increased the AUC and C_{max} of rosuvastatin by 35% and 72%, respectively. Patients taking concomitant medications with disposition dependent upon BCRP and with narrow therapeutic index should be closely monitored for signs of changed tolerability of the concomitant medication as a result of increased exposure whilst receiving TAGRISSO (see section 5.2).

In a clinical PK study, co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and C_{max} of simvastatin by 9% and 23% respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely. Pregnane X Receptor (PXR) regulated enzyme interactions other than CYP3A4 have not been studied. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception for the following periods after completion of treatment with this medicinal product: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

Pregnancy

There are no or limited amount of data from the use of osimertinib in pregnant women. Studies in animals have shown reproductive toxicity (embryo lethality, reduced foetal growth, and neonatal death, see section 5.3). Based on its mechanism of action and preclinical data, osimertinib may cause foetal harm when administered to a pregnant woman. TAGRISSO should not be used during pregnancy unless the clinical condition of the woman requires treatment with osimertinib.

Breast-feeding

It is not known whether osimertinib or its metabolites are excreted in human milk. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. However, osimertinib and its metabolites were detected in the suckling pups and there were adverse effects on pup growth and survival (see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with TAGRISSO.

Fertility

There are no data on the effect of TAGRISSO on human fertility. Results from animal studies have shown that osimertinib has effects on male and female reproductive organs and could impair fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

TAGRISSO has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety data of TAGRISSO reflects exposure from 411 previously treated T790M mutation-positive NSCLC patients who received a dose of 80 mg daily. Comparative safety data from randomised clinical trials are not yet available. Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (42%) and rash (24%). Grade 3 and grade 4 adverse events across both studies were 26% and 1.2%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to ADRs occurred in 2.2% of the patients. Discontinuation due to adverse reactions or abnormal laboratory parameters was 3.2%.

Tabulated list of adverse reactions

Table 2 lists the incidences of adverse reactions commonly reported in patients receiving TAGRISSO.

Adverse drug reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: very common ($\geq 1/10$); common ($> 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data). This section includes only data derived from completed studies where patient exposure is known. Data in Table 2 are cumulative from AURA extension (Phase II) and AURA 2 studies; only events for patients receiving at least one dose of TAGRISSO are summarized.

Table 2. Adverse drug reactions reported in AURA^a studies

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades) ^b	Frequency of CTCAE grade 3-4
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease ^c	Common (2.7%) ^d	0.7%
Gastrointestinal disorders	Diarrhoea	Very common (42%)	1%
	Stomatitis	Very common (12%)	0%
Skin and subcutaneous tissue disorders	Rash ^e	Very common (41%)	0.5%
	Dry skin ^f	Very common (31%)	0%
	Paronychia ^g	Very common (25%)	0%
	Pruritus	Very common (14%)	0%

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades) ^b	Frequency of CTCAE grade 3-4
Investigations (findings based on test results presented as CTCAE grade shifts)	Platelet count decreased ^h	Very common (54%)	1.2%
	Leucocytes decreased ^h	Very common (67%)	1.2%
	Neutrophils decreased ^h	Very common (33%)	3.4%

^a Data is cumulative from AURA extension (Phase II) and AURA 2 studies; only events for patients receiving at least one dose of TAGRISSO are summarized.

^b National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

^c Includes cases reported within the clustered terms: Interstitial lung disease and pneumonitis.

^d 4 CTCAE grade 5 events (fatal) were reported.

^e Includes cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform.

^f Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema.

^g Includes cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasia, onycholysis, onychomadesis, paronychia.

^h Represents the incidence of laboratory findings, not of reported adverse events.

Description of selected adverse reactions

Interstitial lung disease (ILD)

In the Phase II studies, the incidence of ILD was 6.2% in patients of Japanese ethnicity, 1.2% in patients of non-Japanese Asian ethnicity and 2.4% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.7 months (see section 4.4).

QTc interval prolongation

Of the 411 patients in AURAex and AURA2, one patient (less than 1%) was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No arrhythmic events were reported in AURAex or AURA2 (see sections 4.4 and 5.1).

Elderly

Of the total number of patients in clinical studies of osimertinib (N=411), 46% were 65 years of age and older, of whom 13% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had adverse reactions that led to study drug dose modifications (interruptions or reductions) (23% versus 17%). The types of adverse events were similar regardless of age. Older patients experienced more Grade 3 or higher adverse reactions compared to younger patients (32% versus 28%). No overall differences in efficacy were observed between these subjects and younger subjects.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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** listed in [Appendix V](#).

4.9 Overdose

In phase I/II clinical trials a limited number of patients were treated with TAGRISSO daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with TAGRISSO daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR-induced AEs (primarily diarrhoea and skin rash) compared to the 80 mg dose. There is limited experience with accidental overdoses in humans. All cases were isolated incidents of patients taking an additional daily dose of TAGRISSO in error, without any resulting clinical consequences.

There is no specific treatment in the event of TAGRISSO overdose. In case of suspected overdose, TAGRISSO should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01XE35.

Mechanism of action

Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harboring sensitising-mutations (EGFR_m) and TKI-resistance mutation T790M.

Pharmacodynamic effects

In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising-mutant and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC₅₀s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC₅₀s 480 nM to 1.8 µM against phospho-EGFR). *In vivo* oral administration of osimertinib lead to tumour shrinkage in both EGFR_m and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Cardiac electrophysiology

The QTc interval prolongation potential of TAGRISSO was assessed in 210 patients who received osimertinib 80 mg daily in AURA2. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of osimertinib on QTc intervals. A pharmacokinetic analysis predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

Clinical efficacy and safety

Two single-arm, open-label clinical studies, AURAex (Phase II Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation-positive lung cancer who have progressed on prior systemic therapy, including an EGFR TKI active substance. All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to treatment. All patients received TAGRISSO at a dose of 80 mg once daily. The primary efficacy outcome measure of these two trials was objective response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Secondary efficacy outcome measures included Duration of Response (DoR), Disease Control Rate (DCR) and Progression-Free Survival (PFS).

Baseline characteristics of the overall study population (AURAex and AURA2) were as follows: median age 63 years, 13% of patients were ≥ 75 years old, female (68%), White (36%), Asian (60%). All patients received at least one prior line of therapy. 31% (N=129) had received 1 prior line of therapy (EGFR-TKI treatment only), 69% (N=282) had received 2 or more prior lines. 72% of patients were never smokers, 99% of patients had a World Health Organization (WHO) performance status of 0 or 1 and 39% of patients had brain metastases (stable for at least 4 weeks and not requiring corticosteroids). The majority of patients (83%) had visceral metastases at baseline. The median duration of follow up for AURAex was 6.9 months and 6.7 months for AURA2.

AURA (Phase I) was an open-label, single arm dose-escalation and expansion Phase I trial including 271 pre-treated patients with locally advanced or metastatic NSCLC across multiple dose expansion cohorts. The safety and efficacy of 80 mg once-daily TAGRISSO was explored in an expansion cohort of 63 previously-treated patients with centrally confirmed T790M positive NSCLC. Prior treatments included EGFR TKI and chemotherapy. The demographic characteristics of the T790M positive study population (n=63) were median age 60 years, female (62%), White (35%), Asian (59%), World Health Organization (WHO) performance status of 0 or 1 (100%) and never smokers (67%). The number of prior lines of therapy ranged from 1 to 9. The median duration of follow up was 8.2 months. Efficacy results from AURA studies as well as pooled analysis (AURAex and AURA2) are summarized in Table 3.

Table 3. Efficacy results from AURA studies

	Phase I	Phase II		
Efficacy Parameter¹	AURA (PhI Expansion) (N=63)	AURAex (Phase II) (N=201)	AURA2 (N=210)	Overall (N=411)
Objective Response Rate^{2,3} % (95% CI)	62 (48, 74)	61(54, 68)	71 (64, 77)	66 (61, 71)
Duration of Response (DoR)³ Median, Months (95% CI)	9.7 (8.3, NE)	NE (NE, NE)	7.8 (7.1, NE)	NE (8.3, NE)
% DoR greater than 6 months (95% CI)	72 (54,84)	83 (74, 89)	75 (65, 82)	78 (72, 84)
Disease Control Rate (DCR)³ % (95% CI)	95 (86, 99)	90 (85, 94)	91 (87, 95)	91 (88, 94)
Progression-free survival Median, Months (95% CI)	11 (7, 15)	NE (8.1, NE)	8.6 (8.3, 9.7)	9.7 (8.3, NE)

¹ Based on BICR, Blinded Independent Central Review, PFS follow-up.

² Objective Response Rate determined by RECIST v1.1 by BICR in the evaluable for response population (measurable disease at baseline by BICR) n=60,199,199,398 for AURA, AURAex, AURA2 and Overall respectively; NE, not estimable, includes 2 complete responses.

³ Based on patients with response only; DoR defined as the time from the date of first documented response (confirmed complete response or partial response, or stable disease ≥ 6 weeks).

Objective response rates above 50% were observed in all predefined subgroups analyzed, including line of therapy, ethnicity, age and region.

In the overall population, 86% (227/263) had documentation of response at the time of the first scan (6 weeks); 96% (253/263) had documentation of response at the time of the second scan (12 weeks).

Clinical studies have not been conducted in patients with de novo EGFR T790M mutation-positive NSCLC.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with TAGRISSO in all subsets of the paediatric population in NSCLC (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterized in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.2 L/h, apparent volume of distribution is 986 L and terminal half-life of approximately 48 hours. The AUC and C_{max} increased dose proportionally over 20 to 240 mg dose range. Administration of osimertinib once daily results in approximately 3 fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady-state, circulating plasma concentrations are typically maintained within a 1.6 fold range over the 24-hour dosing interval.

Absorption

Following oral administration of TAGRISSO, peak plasma concentrations of osimertinib were achieved with a median (min-max) t_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of TAGRISSO has not been determined. Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase by 6% (90% CI -5, 19) and C_{max} decrease by 7% (90% CI -19, 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

Population estimated mean volume of distribution at steady-state (V_{ss}/F) of osimertinib is 986 L indicating extensive distribution into tissue. Plasma protein binding could not be measured due to instability, but based on the physicochemical properties of osimertinib plasma protein binding is likely to be high. Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes.

Biotransformation

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. CYP3A4 mediated metabolism may be a minor pathway. Alternative metabolic pathways may exist which have not been fully characterized. Based on *in vitro* studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to TAGRISSO while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of TAGRISSO to patients,

with a median (min-max) t_{\max} of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady-state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. At least 12 components were observed in the pooled urine and faecal samples in humans with 5 components accounting for >1% of the dose of which unchanged osimertinib, AZ5104 and AZ7550, accounted for approximately 1.9, 6.6 and 2.7% of the dose while a cysteinyl adduct (M21) and an unknown metabolite (M25) accounted for 1.5% and 1.9% of the dose, respectively.

Based on *in vitro* studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Based on *in vitro* studies, osimertinib is not an inhibitor of UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Elimination

Following a single oral dose of 20 mg, 67.8% of the dose was recovered in faeces (1.2% as parent) while 14.2% of the administered dose (0.8% as parent) was found in urine by 84 days of sample collection. Unchanged osimertinib accounted for approximately 2% of the elimination with 0.8% in urine and 1.2% in faeces.

Interactions with transport proteins

In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3. *In vitro*, osimertinib does not inhibit OAT1, OAT3, OATP1B1, OATP1B3 and MATE2K at clinically relevant concentrations. However, interactions with MATE1 and OCT2 substrates cannot be excluded.

Effects of osimertinib on P-gp and BCRP

Based on *in vitro* studies, osimertinib is a substrate of P-glycoprotein and breast cancer resistant protein (BCRP), but is unlikely to result in clinically relevant drug interactions with active substances by osimertinib at the clinical doses. Based on *in vitro* data, osimertinib is an inhibitor of BCRP and P-gp. PXR regulated enzyme interactions other than CYP3A4 have not been studied (See section 4.5).

Special populations

In a population based pharmacokinetic analyses (n=778), no clinically significant relationships were identified between predicted steady-state exposure (AUC_{ss}) and patient's age (range: 21 to 89 years), gender, ethnicity (including White, Asian, Japanese, Chinese and non-Asian-non-White patients) and smoking status (n=24 current smokers, n=232 former smokers). Population PK analysis indicated that body weight was a significant covariate with a -20% to +30% change in osimertinib AUC_{ss} expected across a body weight range of 90kg to 43kg respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median body weight of 62 kg. Taking the extremes of body weight into consideration, from <43 kg to >90 kg, AZ5104 metabolite ratios ranged from 11.8% to 9.6% while for AZ7550 it ranged from 12.8% to 9.9%, respectively. These exposure changes due to body weight differences are not considered clinically relevant.

Hepatic impairment

Osimertinib is eliminated mainly via the liver, and hence, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in subjects with hepatic impairment has not been conducted. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying malignancy,

>5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 44 patients with mild hepatic impairment and 330 patients with normal hepatic function osimertinib exposures were similar. There are limited data available on patients with hepatic impairment (see section 4.2).

Renal impairment

A pharmacokinetic study in patients with renal impairment has not been conducted. Based on a population pharmacokinetic analysis of 330 patients with mild renal impairment (CL_{cr} 60 to less than 90 mL/min), 149 patients with moderate renal impairment (CL_{cr} 30 to <than 60 mL/min), 3 patients with severe renal impairment (CL_{cr} 15 to <than 30 mL/min) and 295 patients with normal renal function (\geq 90 mL/min), osimertinib exposures were similar. Severe renal impairment may influence the elimination of hepatically eliminated medicinal products. Patients with CL_{cr} less than 15 mL/min were not included in the clinical trials.

5.3 Preclinical safety data

The main findings observed in repeat dose toxicity studies in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing with the exception of partial recovery for some of the corneal changes.

Non-clinical data indicate that osimertinib and its metabolite (AZ5104) inhibit the h-ERG channel, and QTc prolonging effect cannot be excluded.

Carcinogenesis and mutagenesis

Carcinogenicity studies have not been performed with osimertinib. Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays.

Reproductive toxicity

Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for \geq 1 month and there was a reduction in male fertility in rats following exposure to osimertinib for 3 months. These findings were seen at clinically relevant plasma concentrations. Pathology findings in the testes seen following 1 month dosing were reversible in rats; however, a definitive statement on reversibility of these lesions in dogs cannot be made.

A female fertility study has not been conducted. In repeat dose toxicity studies, an increased incidence of anoestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for \geq 1 month at clinically relevant plasma concentrations. Findings in the ovaries seen following 1 month dosing were reversible.

In a modified embryofetal development study in the rat, osimertinib caused embryoletality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced foetal weights but no adverse effects on external or visceral foetal morphology. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable exposure to osimertinib and its metabolites in suckling pups plus a reduction in pup survival and poor pup growth (at doses of 20 mg/kg and above).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol
Microcrystalline cellulose
Low-substituted hydroxypropyl cellulose
Sodium stearyl fumarate

Tablet coating

Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/Al perforated unit dose blisters. Cartons of 30 x 1 tablets (3 blister strips).

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
Gärtnavägen
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1086/001
EU/1/16/1086/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Lonza AG
Walliser Werke
Postfach
CH-3930 Visp
Switzerland

Name and address of the manufacturer(s) responsible for batch release

AstraZeneca AB
Gartnavagen
SE-15185 Sodertalje
SWEDEN

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy.	30 June 2017

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40 mg film-coated tablets
osimertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg osimertinib (as mesylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1086/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tagrisso 40 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 80 mg film-coated tablets
osimertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg osimertinib (as mesylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1086/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tagrisso 80 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSE 40 mg tablets
osimertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSE 80 mg tablets
osimertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

TAGRISSE 40 mg tablets **TAGRISSE 80 mg tablets** Osimertinib

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TAGRISSE is and what it is used for
2. What you need to know before you take TAGRISSE
3. How to take TAGRISSE
4. Possible side effects
5. How to store TAGRISSE
6. Contents of the pack and other information

1. What TAGRISSE is and what it is used for

TAGRISSE contains the active substance osimertinib which belongs to the protein kinase inhibitor class of anticancer medicines. TAGRISSE is used to treat adults with a type of lung cancer called ‘non-small cell lung cancer.’ It is used when:

- You test positive for a ‘T790M mutation’ – see ‘How TAGRISSE works.’
- Your cancer is advanced and is worsening despite previous treatments, including a medicine which worked to block ‘EGFR’ (epidermal growth factor receptor).

How TAGRISSE works

- A test has shown that your cancer is linked to a specific change in the EGFR gene called ‘T790M.’ This is known as a T790M mutation.
- Because of this T790M mutation, medicines that block EGFR may no longer work.
- TAGRISSE affects T790M and may help to slow or stop your lung cancer growing. It may also help to shrink the tumour.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take TAGRISSO

Do not take TAGRISSO if:

- you are allergic (hypersensitive) to osimertinib or any of the other ingredients of this medicine (listed in section 6).
- you are taking St. John's wort (*Hypericum perforatum*).

If you are not sure, talk to your doctor, pharmacist or nurse before taking TAGRISSO.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking TAGRISSO if:

- you have suffered from inflammation of your lungs (a condition called 'interstitial lung disease')
- you have ever had heart problems – your doctor may want keep a close eye on you.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

Tell your doctor straight away while taking this medicine if:

- you have sudden difficulty in breathing together with a cough or fever. See 'Serious side effects' in section 4 for more information.

Children and adolescents

TAGRISSO has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and TAGRISSO

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription. This is because TAGRISSO can affect the way some other medicines work. Also some other medicines can affect the way TAGRISSO works.

Tell your doctor before taking TAGRISSO if you are taking any of the following medicines:

The following medicines may reduce how well TAGRISSO works:

- Phenytoin, carbamazepine or phenobarbital – used for seizures or fits.
- Rifabutin or rifampicin – used for tuberculosis (TB).
- St. John's wort (*Hypericum perforatum*) – an herbal medicine used for depression.

TAGRISSO may affect how well the following medicine works and/or increase side effects of these medicines:

- Warfarin – used for blood clots.
- Phenytoin and S-mephenytoin – used for seizures or fits.
- Alfentanil, fentanyl and other painkillers used for operations.
- Rosuvastatin - used to lower cholesterol.
- Oral hormonal contraceptive pill – used to prevent pregnancy.
- Bosentan – used for high blood pressure in the lungs.
- Efavirenz and etravirine – used to treat HIV infections/AIDS.
- Modafinil – used for sleep disorders.

If you are taking any of the medicines listed above, tell your doctor before taking TAGRISSO.

Your doctor will discuss appropriate treatment options with you.

Pregnancy – information for women

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. If you do become pregnant during treatment, tell your doctor straight away. Your doctor will decide with you whether you should carry on taking TAGRISSO.
- You should not become pregnant while taking this medicine. If you are able to become pregnant, you must use effective contraception. See ‘Contraception - information for women and men’ below.
- If you plan to become pregnant after taking the last dose of this medicine, ask your doctor for advice. This is because some medicine may remain in your body. (see advice on contraception, below)

Pregnancy – information for men

- If your partner becomes pregnant while you are taking this medicine, tell your doctor straight away.

Contraception – information for women and men

You must use effective contraception during treatment.

- TAGRISSO may interfere with how well oral hormonal contraceptives work. Discuss with your doctor the most appropriate methods of contraception
- TAGRISSO may pass into semen. Therefore, it is important that men also use effective contraception.

You must also do this after completing treatment with TAGRISSO:

- **Women** – keep using contraception for 2 months after.
- **Men** – keep using contraception for 4 months after.

Breast-feeding

Do not breast-feed while taking this medicine. This is because it is not known if there is a risk to your baby.

Driving and using machines

TAGRISSO has no or no marked influence on the ability to drive and use machines.

3. How to take TAGRISSO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

- The recommended dose is one 80 mg tablet each day.
- If necessary, your doctor may reduce your dose to one 40 mg tablet each day.

How to take

- TAGRISSO is taken by mouth. Swallow the tablet whole with water. Do not crush, split or chew the tablet.
- Take TAGRISSO every day at about the same time.
- You can take this medicine with or without food.

If you have trouble swallowing the tablet, you can mix it in water:

- Put the tablet in a glass.
- Add 50 mL (about two-thirds of a tumblerful) of still (non-fizzy) water – do not use any other liquids.

- Stir the water until the tablet breaks up into very small pieces - the tablet will not completely dissolve.
- Drink the liquid straight away.
- To make sure you have taken all of the medicine, rinse the glass thoroughly with another 50 mL of water and drink it.

If you take more TAGRISSO than you should

If you take more than your normal dose, contact your doctor or nearest hospital straight away.

If you forget to take TAGRISSO

If you forget a dose, take it as soon as you remember it. However, if it is less than 12 hours until your next dose is due, skip the missed dose. Take your next normal dose at its scheduled time.

If you stop taking TAGRISSO

Do not stop taking this medicine - talk to your doctor first. It is important to take this medicine every day, for as long as your doctor prescribes it for you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

Serious side effects

Tell your doctor straight away if you notice the following serious side effect:

- Sudden difficulty in breathing together with a cough or fever - this may be a sign of inflamed lungs (a condition called ‘interstitial lung disease’) and can be fatal in some cases. Your doctor may wish to stop TAGRISSO if you get this side effect. This side effect is common: it may affect up to 1 in 10 people.

Tell your doctor straight away if you notice the serious side effect listed above.

Other side effects

Very common (may affect more than 1 in 10 people)

- Diarrhoea - this may come and go during treatment. Tell your doctor if your diarrhoea does not go away or becomes severe.
- Skin and nail problems - signs may include itching, dry skin, rash, redness around the fingernails. This is more likely in areas exposed to the sun. Using moisturisers regularly on your skin and nails can help with this. Tell your doctor if your skin or nail problems get worse.
- Stomatitis - inflammation of the inner lining of the mouth.
- Abnormal decrease in the number of white blood cells (leukocytes or neutrophils).
- Reduction in the number of platelets in the blood.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TAGRISSO

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date (EXP) which is stated on the blister foil and carton. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TAGRISSO contains

- The active substance is osimertinib (as mesylate). Each 40 mg film-coated tablet contains 40 mg of osimertinib. Each 80 mg film-coated tablet contains 80 mg of osimertinib.
- The other ingredient(s) are mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, yellow iron oxide, red ironoxide, black iron oxide.

What TAGRISSO looks like and contents of the pack

TAGRISSO 40 mg is supplied as beige, film-coated, round and biconvex tablets, marked with “AZ” and “40” on one side, and plain on the other.

TAGRISSO 80 mg is supplied as beige, film-coated, oval and biconvex tablets, marked with “AZ” and “80” on one side, and plain on the other.

TAGRISSO is supplied in blisters containing 30 x 1 film-coated tablets, packed in cartons containing 3 blisters strips of 10 tablets each.

Marketing Authorisation Holder and Manufacturer

AstraZeneca AB
Gärtnavägen
SE-151 85 Södertälje
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Lietuva

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United Kingdom
AstraZeneca UK Ltd
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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Annex IV

**Conclusions on the granting of the conditional marketing authorisation presented by the
European Medicines Agency**

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.