**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use TAGRISSO safely and effectively. See full prescribing information for TAGRISSO.**

**TAGRISSO® (osimertinib) tablets, for oral use**
**Initial U.S. Approval: 2015**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Dosage and Administration (2.4) | 3/2017 |
| Warnings and Precautions (5.4) | 3/2017 |

**---------- INDICATIONS AND USAGE ----------**

TAGRISSO is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR TKI therapy. (1)

**---------- DOSAGE AND ADMINISTRATION ----------**

- Confirm the presence of T790M mutation in tumor or, in the absence of tumor, plasma specimens prior to initiation of treatment with TAGRISSO. (2.1)
- 80 mg orally once daily, with or without food. (2.2)

**---------- DOSAGE FORMS AND STRENGTHS ----------**

Tablets: 80 mg and 40 mg (3)

**---------- CONTRAINDICATIONS ----------**

None. (4)

**---------- WARNINGS AND PRECAUTIONS ----------**

- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 3.5% of patients. Permanently discontinue TAGRISSO in patients diagnosed with ILD/Pneumonitis. (5.1)
- QTc Interval Prolongation: Monitor electrocardiograms and electrolytes in patients who have a history or predisposition for QTc prolongation, or those who are taking medications that are known to prolong the QTc interval. Withhold then restart at a reduced dose or permanently discontinue TAGRISSO. (2.4, 5.2)
- Cardiomyopathy: Occurred in 1.9% of patients. Conduct cardiac monitoring, including left ventricular ejection fraction (LVEF) assessment in patients with cardiac risk factors. (2.4, 5.3)
- Keratitis: Promptly refer patients with signs and symptoms of keratitis to an ophthalmologist for evaluation. (5.4)
- Embryo-Fetal Toxicity: TAGRISSO can cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with TAGRISSO and for 6 weeks after final dose. Advise males to use effective contraception for 4 months, after the last dose of TAGRISSO. (5.5, 8.1, 8.3)

**---------- ADVERSE REACTIONS ----------**

Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, and fatigue. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or www.TAGRISSO.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**---------- DRUG INTERACTIONS ----------**

Strong CYP3A Inducers: Avoid if possible. If not possible, increase TAGRISSO to 160 mg daily in patients receiving a strong CYP3A4 inducer. (2.4, 7.1)

**----------USE IN SPECIFIC POPULATIONS----------**

Lactation: Do not breastfeed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: X/2017**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed.

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Patient Selection

Confirm the presence of a T790M EGFR mutation in tumor or plasma specimens prior to initiation of treatment with TAGRISSO *[see Indications and Usage (1) and Clinical Studies (14)]*. Testing for the presence of the mutation in plasma specimens is recommended only in patients for whom a tumor biopsy cannot be obtained. If this mutation is not detected in a plasma specimen, re-evaluate the feasibility of biopsy for tumor tissue testing. Information on FDA-approved tests for the detection of T790M mutations is available at http://www.fda.gov/companiondiagnostics.

### 2.2 Recommended Dosage Regimen

The recommended dose of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

### 2.3 Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces of) water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

## 2.4 Dosage Modification

Adverse Reactions

**Table 1. Recommended Dose Modifications for TAGRISSO**

| Target Organ | Adverse Reaction[a] | Dose Modification |
|---|---|---|
| *Pulmonary* | Interstitial lung disease (ILD)/Pneumonitis | Permanently discontinue TAGRISSO. |
| *Cardiac* | QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b] | 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 resume at 40 mg dose. |
| | QTc interval prolongation with signs/symptoms of life-threatening arrhythmia | Permanently discontinue TAGRISSO. |
| | Symptomatic congestive heart failure or asymptomatic left ventricular dysfunction that persists ≥ 4 weeks | Permanently discontinue TAGRISSO. |
| *Other* | Adverse reaction of Grade 3 or greater severity | Withhold TAGRISSO for up to 3 weeks. |
| | If improvement to Grade 0-2 within 3 weeks | Resume at 80 mg or 40 mg daily. |
| | If no improvement within 3 weeks | Permanently discontinue TAGRISSO. |

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

*Strong CYP3A4 Inducers*
If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when coadministering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

80 mg tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse.

40 mg tablets: beige, round and biconvex tablet marked with "AZ 40" on one side and plain on the reverse.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

The following information for ILD/ Pneumonitis, QTc Interval Prolongation, Cardiomyopathy and Keratitis reflects exposure to TAGRISSO in 833 patients with EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who received TAGRISSO at the recommended dose of 80 mg once daily in AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143).

### 5.1 Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.5% (n=29) of TAGRISSO-treated patients (n=833); 0.6% (n=5) of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6)]*.

### 5.2 QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 833 patients treated with TAGRISSO in clinical trials, 0.7% (n=6) were found to have a QTc greater than 500 msec, and 2.9% of patients (n=24) had an increase from baseline QTc greater than 60 msec *[see Clinical Pharmacology (12.2)]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of greater than 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4)]*.

### 5.3 Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 1.9% (n=16) of 833 TAGRISSO-treated patients: 0.1% (n=1) of cases were fatal.

Left Ventricular Ejection Fraction (LVEF) decline greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including an assessment of LVEF at baseline and during treatment in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4)]*.

### 5.4 Keratitis

Keratitis was reported in 0.7% (n=6) of 833 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

### 5.5 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended human dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5-times those observed in patients at the 80 mg dose level.

Advise pregnant women of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1), (8.3) and Clinical Pharmacology (12.3)]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*

Cardiomyopathy *[see Warnings and Precautions (5.3)]*

Keratitis *[see Warnings and Precautions (5.4)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to TAGRISSO (80 mg daily) in patients with EGFR T790M mutation-positive metastatic NSCLC in an open-label, randomized, active-controlled trial (AURA3, n=279) and in two single arm trials, AURA Extension (n=201) and AURA2 (n=210). Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required: steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from trial enrollment.

AURA3 Trial

The safety of TAGRISSO was evaluated in AURA3, a multicenter international open label randomized (2:1) controlled trial conducted in 419 patients with unresectable or metastatic EGFR T790M mutation-positive NSCLC who had progressive disease following first line EGFR TKI treatment. A total of 279 patients received TAGRISSO 80 mg orally once daily until intolerance to therapy, disease progression, or investigator determination that the patient was no longer benefiting from treatment. A total of 136 patients received pemetrexed plus either carboplatin or cisplatin every three weeks for up to 6 cycles; patients without disease progression after 4 cycles of chemotherapy could continue maintenance pemetrexed until disease progression, unacceptable toxicity, or investigator determination that the patient was no longer benefiting from treatment. Left Ventricular Ejection Fraction (LVEF) was evaluated at screening and every 12 weeks. The median duration of treatment was 8.1 months for patients treated with TAGRISSO and 4.2 months for chemotherapy-treated patients. The trial population characteristics were: median age 62 years, age less than 65 (58%), female (64%), Asian (65%), never smokers (68%), and ECOG PS 0 or 1 (100%).

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (41%), rash (34%), dry skin (23%), nail toxicity (22%), and fatigue (22%). Serious adverse reactions were reported in 18% of patients treated with TAGRISSO and 26% in the chemotherapy group. No single serious adverse reaction was reported in 2% or more patients treated with TAGRISSO. One patient (0.4%) treated with TAGRISSO experienced a fatal adverse reaction (ILD/pneumonitis).

Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (1.8%), neutropenia (1.1%), and diarrhea (1.1%). Adverse reactions resulting in permanent discontinuation of TAGRISSO occurred in 7% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in TAGRISSO-treated patients in AURA3. AURA3 was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in AURA3**

| Adverse Reaction | TAGRISSO (N=279) | | Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=136) | |
|---|---|---|---|---|
| | All Grades[a] (%) | Grade 3/4[a] (%) | All Grades[a] (%) | Grade 3/4[a] (%) |
| **Gastrointestinal disorders** | | | | |
| Diarrhea | 41 | 1.1 | 11 | 1.5 |
| Nausea | 16 | 0.7 | 49 | 3.7 |
| Stomatitis | 15 | 0 | 15 | 1.5 |
| Constipation | 14 | 0 | 35 | 0 |
| Vomiting | 11 | 0.4 | 20 | 2.2 |
| **Skin disorders** | | | | |
| Rash[b] | 34 | 0.7 | 5.9 | 0 |
| Dry skin[c] | 23 | 0 | 4.4 | 0 |
| Nail toxicity[d] | 22 | 0 | 1.5 | 0 |
| Pruritus[e] | 13 | 0 | 5.1 | 0 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 18 | 1.1 | 36 | 2.9 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Cough | 17 | 0 | 14 | 0 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Back pain | 10 | 0.4 | 9 | 0.7 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue[f] | 22 | 1.8 | 40 | 5.1 |

* NCI CTCAE v4.0.

[a] No grade 4 events were reported.

[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and acneform dermatitis.

[c] Includes dry skin, eczema, skin fissures, xerosis.
[d] Includes nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, nail toxicity, onychoclasis, onycholysis, onychomadesis, paronychia.
[e] Includes pruritus, pruritus generalized, eyelid pruritus.
[f] Includes fatigue, asthenia.

**Table 3. Common Laboratory Abnormalities (>20% for all NCI CTCAE Grades) in AURA3**

| Laboratory Abnormality | TAGRISSO (N=279) | | Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131[a]) | |
|---|---|---|---|---|
| | Change from Baseline All Grades (%) | Change from Baseline to Grade 3 or Grade 4 (%) | Change from Baseline All Grades (%) | Change from Baseline to Grade 3 or Grade 4 (%) |
| Leukopenia | 61 | 1.1 | 75 | 5.3 |
| Lymphopenia | 63 | 8.2 | 61 | 9.9 |
| Thrombocytopenia | 46 | 0.7 | 48 | 7.4 |
| Neutropenia | 27 | 2.2 | 49 | 12 |

[a] Based on the number of patients with available follow-up laboratory data

AURA Extension and AURA2 Trials

The safety of TAGRISSO was evaluated in two single arm trials, AURA Extension (n=201) and AURA2 (n=210). A total of 411 patients with EGFR 790M mutation-positive NSLC who received one or more prior EGFR therapies including an EGFR TKI were treated with TAGRISSO (80 mg daily). The majority of patients were heavily pretreated. Prior to enrollment, 68% of patients had received at least 2 prior treatment regimens, 46% had received 3 or more prior lines of therapy, and 63% had received prior platinum-based chemotherapy.

Median duration of exposure to TAGRISSO was 7.7 months (range: <0.1 to 11.6 months). The toxicity profile of TAGRISSO observed in the AURA Extension and AURA2 trials was generally consistent with the toxicity profile observed in the AURA3 trial. Four patients (1%) treated with TAGRISSO developed fatal adverse reactions of ILD/pneumonitis. Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients treated with TAGRISSO. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis.

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Coadministering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3)]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid coadministering TAGRISSO with strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, St. John's Wort) [note: effect of St. John's Wort varies widely and is preparation-dependent]. Increase the TAGRISSO dosage when coadministering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4)]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

### 7.2 Effect of Osimertinib on Other Drugs

Coadministering TAGRISSO with a BCRP substrate increased the exposure of the BCRP substrate compared to administering the BCRP substrate alone *[see Clinical Pharmacology (12.3)]*. Increased BCRP substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP substrate (e.g., rosuvastatin, sulfasalazine, topotecan), unless otherwise instructed in its approved labeling, when coadministered with TAGRISSO.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary*

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended human dose *[see Data]*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

*Data*

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1-times the AUC observed in patients at the recommended dose

of 80 mg), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

### 8.2 Lactation

Risk Summary

There are no data on the presence of osimertinib in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1)]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

### 8.3 Females and Males of Reproductive Potential

Contraception

*Females*

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1)]*.

*Males*

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1)]*.

### 8.4 Pediatric Use

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

### 8.5 Geriatric Use

Three hundred and forty-six (42%) of the 833 patients in AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and an expansion cohort in the first-in-human trial of osimertinib (AURA1, n=143) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (9.8% versus 6.8%)

and more frequent dose modifications for adverse reactions (10.1% versus 6.0%) in patients 65 years or older as compared to those younger than 65 years.

### 8.6 Renal Impairment

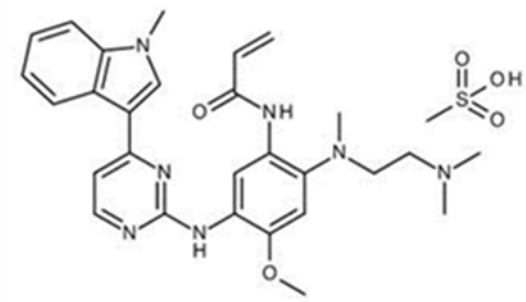
No dose adjustment is recommended in patients with mild, [creatinine clearance (CLcr) 60-89 mL/min, as estimated by the Cockcroft Gault method (C-G)] moderate, (CLcr 30-59 mL/min, as estimated by C-G) or severe (CLcr 15-29 mL/min) renal impairment. There is no recommended dose of TAGRISSO for patients with end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

### 8.7 Hepatic Impairment

No dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST] or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

## 11 DESCRIPTION

Osimertinib is a kinase inhibitor for oral use. The molecular formula for osimertinib mesylate is $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$, and the molecular weight is 596 g/mol. The chemical name is N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt. Osimertinib has the following structural formula (as osimertinib mesylate):



TAGRISSO tablets contain 40 or 80 mg of osimertinib, equivalent to 47.7 and 95.4 mg of osimertinib mesylate, respectively. Inactive ingredients in the tablet core are mannitol, microcrystalline cellulose, low-substituted hydroxpropyl cellulose and sodium stearyl fumarate. The tablet coating consists of polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, ferric oxide yellow, ferric oxide red and ferric oxide black.

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

Osimertinib is a kinase inhibitor of the epidermal growth factor receptor (EGFR), which binds irreversibly to certain mutant forms of EGFR (T790M, L858R, and exon 19 deletion) at approximately 9-fold lower concentrations than wild-type. Two pharmacologically-active metabolites (AZ7550 and AZ5104 circulating at approximately 10% of the parent) with similar inhibitory profiles to osimertinib have been identified in the plasma after oral administration of osimertinib. AZ7550 showed a similar potency to osimertinib, while AZ5104 showed greater potency against exon 19 deletion and T790M mutants (approximately 8-fold) and wild-type (approximately 15-fold) EGFR. *In vitro*, osimertinib also inhibited the activity of HER2, HER3, HER4, ACK1, and BLK at clinically relevant concentrations.

In cultured cells and animal tumor implantation models, osimertinib exhibited anti-tumor activity against NSCLC lines harboring EGFR-mutations (T790M/L858R, L858R, T790M/exon 19 deletion, and exon 19 deletion) and, to a lesser extent, wild-type EGFR amplifications. Osimertinib distributed to the brain in multiple animal species (monkey, rat, and mouse) with brain to plasma AUC ratios of approximately 2 following oral dosing. These data are consistent with observations of tumor regression and increased survival in osimertinib- versus control-treated animals in a pre-clinical mutant-EGFR intracranial mouse metastasis xenograft model (PC9; exon 19 del).

## 12.2 Pharmacodynamics

Based on an analysis of dose-exposure response relationships over the dose range of 20 mg (0.25 times the recommended dose) to 240 mg (3 times the recommended dose), no apparent relationship between osimertinib exposure and objective response rate, duration of response and progression-free survival was identified; however, there were limited data available at the 20 mg dose. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhea and ILD.

Cardiac Electrophysiology

The QTc interval prolongation potential of osimertinib was assessed in 210 patients who received TAGRISSO 80 mg daily in AURA2. A central tendency analysis of the QTcF data at steady-state demonstrated that the maximum mean change from baseline was 16.2 msec (upper bound of two-sided 90% confidence interval (CI) 17.6 msec). A pharmacokinetic/pharmacodynamic analysis in AURA2 suggested a concentration-dependent QTc interval prolongation of 14 msec (upper bound of two-sided 90% CI: 16 msec) at a dose of TAGRISSO 80 mg.

## 12.3 Pharmacokinetics

The area under the plasma concentration-time curve (AUC) and maximal plasma concentration ($C_{max}$) of osimertinib increased dose proportionally over 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) after oral administration and exhibited linear pharmacokinetics (PK). Administration of TAGRISSO orally once daily resulted in approximately 3-fold accumulation with steady-state exposures achieved after 15 days of dosing. At steady state, the $C_{max}$ to $C_{min}$ (minimal concentration) ratio was 1.6-fold.

Absorption

The median time to $C_{max}$ of osimertinib was 6 hours (range 3-24 hours).

Following administration of a 20 mg TAGRISSO tablet with a high-fat, high-calorie meal (containing approximately 58 grams of fat and 1000 calories), the $C_{max}$ and AUC of osimertinib were comparable to that under fasting conditions.

Distribution

The mean volume of distribution at steady-state ($V_{ss}/F$) of osimertinib was 997 L. Plasma protein binding of osimertinib was 95%.

Elimination

Osimertinib plasma concentrations decreased with time and a population estimated mean half-life of osimertinib was 48 hours, and oral clearance (CL/F) was 14.2 (L/h).

Metabolism

The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation in vitro. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after TAGRISSO oral administration. The geometric mean exposure (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state.

Excretion

Osimertinib is primarily eliminated in the feces (68%) and to a lesser extent in the urine (14%). Unchanged osimertinib accounted for approximately 2% of the elimination.

Specific Populations

No clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, baseline albumin, smoking status, mild (CLcr 60-89 mL/min, as estimated by C-G), moderate (CLcr 30-59 mL/min, as estimated by C-G), or severe (CLcr 15-29 mL/min) renal impairment, or mild (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin between 1 to 1.5 times ULN and any AST) or moderate (total bilirubin between 1.5 to 3 times ULN and any AST) hepatic impairment. The pharmacokinetics of osimertinib in patients with end-stage renal disease (CLcr less than 15 mL/min) or with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) are unknown.

Drug Interactions

*Effect of Other Drugs on TAGRISSO in Clinical Pharmacokinetic Studies*

*Strong CYP3A Inducers:* The steady-state AUC of osimertinib was reduced by 78% in patients when coadministered with rifampin (600 mg daily for 21 days) in a clinical pharmacokinetic study *[see Drug Interactions (7.1)]*.

*Strong CYP3A Inhibitors:* Coadministering TAGRISSO with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib (AUC increased by 24% and $C_{max}$ decreased by 20%).

*Gastric Acid Reducing Agents:* The exposure of osimertinib was not affected by concurrent administration of a single 80 mg TAGRISSO tablet following 40 mg omeprazole administration for 5 days.

*Effect of Osimertinib on Other Drugs in Clinical Pharmacokinetic Studies*

*BCRP substrates:* Coadministering TAGRISSO with rosuvastatin (a BCRP substrate) increased rosuvastatin AUC by 35% and $C_{max}$ by 72% in a clinical pharmacokinetic study *[see Drug Interactions (7.2)]*.

*CYP3A4 substrates:* Coadministering TAGRISSO with simvastatin (a CYP3A4 substrate) had no clinically significant effect on the exposure of simvastatin in a clinical pharmacokinetic study.

*In Vitro Studies*

*CYP450 Metabolic Pathways:* Osimertinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1. Osimertinib induced CYP1A2 enzymes.

*Transporter Systems:* Osimertinib is a substrate of P-glycoprotein and BCRP and is not a substrate of OATP1B1 and OATP1B3. Osimertinib is an inhibitor of BCRP and does not inhibit P-glycoprotein, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Based on studies in animals, male fertility may be impaired by treatment with TAGRISSO. Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for 1 month or more with evidence of reversibility in the rat. Following administration of osimertinib to rats for approximately 10 weeks at a dose of 40 mg/kg, at exposures 0.5-times the AUC observed in patients at the recommended dose of 80 mg, there was a reduction in male fertility, demonstrated by increased pre-implantation loss in untreated females mated to treated males.

Based on studies in animals, female fertility may be impaired by treatment with TAGRISSO. In repeat dose toxicity studies, histological evidence of anestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for 1 month or more at exposures 0.3-times the AUC observed in patients at the recommended dose of 80 mg. Findings in the ovaries seen following 1 month of dosing exhibited evidence of reversibility. In a female fertility study in rats, administration of osimertinib from 2 weeks prior to mating through Day 8 of gestation at a dose of 20 mg/kg/day (approximately 1.5-times the human $C_{max}$ at the recommended dose of 80 mg/day) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic

deaths. These findings showed evidence of reversibility when females were mated 1 month after treatment discontinuation.

## 14 CLINICAL STUDIES

AURA3 Trial

The efficacy of TAGRISSO was demonstrated in a randomized, multicenter open-label, active-controlled trial in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI (AURA3). 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 randomization.

A total of 419 patients were randomized 2:1 to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomization was stratified by ethnicity (Asian vs. non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, disease progression, or investigator determination that the patient was no longer benefiting from treatment. Patients in the chemotherapy arm received pemetrexed 500 mg/m$^2$ with carboplatin AUC5 or pemetrexed 500mg/m$^2$ with cisplatin 75 mg/m$^2$ on Day 1 of every 21-day cycle for up to 6 cycles. Patients whose disease had not progressed after four cycles of platinum-based chemotherapy could have received pemetrexed maintenance therapy (pemetrexed 500 mg/m$^2$ on Day 1 of every 21-day cycle).

The major efficacy outcome measure was progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) by investigator assessment. Additional efficacy outcome measures included objective response rate (ORR), duration of response (DoR), and overall survival (OS). Patients randomized to the chemotherapy arm who had radiological progression according to both investigator and blinded independent central review (BICR) were permitted to cross over to receive treatment with TAGRISSO.

The baseline demographic and disease characteristics of the overall trial population were: median age 62 years (range: 20-90 years), ≥75 years old (15%), female (64%), White (32%), Asian (65%), never smoker (68%), WHO performance status 0 or 1 (100%). Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with central nervous system (CNS) metastases (including 11% with measurable CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

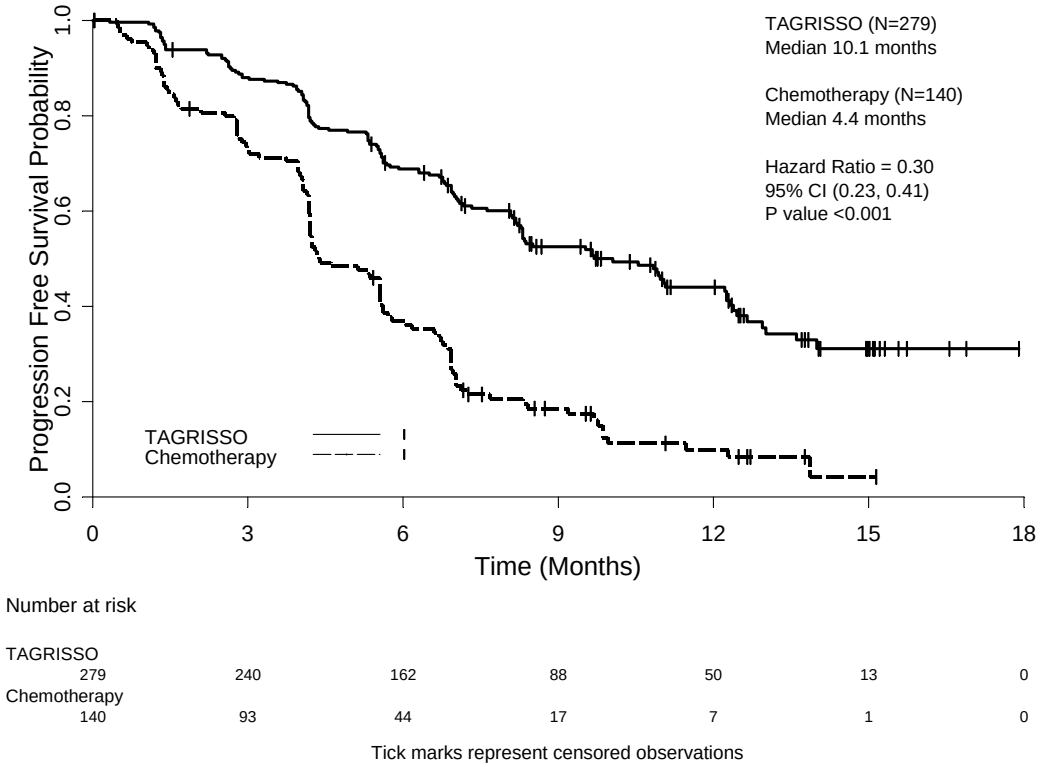
In AURA3, there was a statistically significant improvement in PFS in the patients randomized to TAGRISSO compared to chemotherapy (See Table 4 and Figure 1). Overall survival data were not mature at the time of the PFS analysis.

**Table 4. AURA3 Efficacy Results According to Investigator Assessment**

| **Efficacy Parameter** | **TAGRISSO (N=279)** | **Chemotherapy (N=140)** |
|---|---|---|
| **Progression-Free Survival** | | |
| Number of events (%) | 140 (50) | 110 (79) |
| Progressive disease | 129 (46) | 104 (74) |
| Death[a] | 11 (4) | 6 (4) |
| Median PFS in months (95% CI) | 10.1 (8.3, 12.3) | 4.4 (4.2, 5.6) |
| Hazard Ratio (95% CI)[b, c] | 0.30 (0.23,0.41) | |
| P-value[b, d] | <0.001 | |
| **Objective Response Rate[e]** | | |
| Objective Response Rate | 65% | 29% |
| (95% CI)[b, f] | (59%, 70%) | (21%, 37%) |
| Complete response | 1% | 1% |
| Partial response | 63% | 27% |
| P-value | <0.001 | |
| **Duration of Response (DoR)** | | |
| Median Duration of Response in months (95% CI) | 11.0 (8.6, 12.6) | 4.2 (3.0, 5.9) |

[a] Without documented radiological disease progression
[b] Stratified by ethnicity (Asian vs. non-Asian)
[c] Pike estimator
[d] Stratified log-rank test
[e] Confirmed
[f] Chi-square test

**Figure 1. Kaplan-Meier Curves of PFS by Investigator Assessment in AURA3**




In a sensitivity analysis of PFS according to blinded independent central review, median PFS was 11 months in the TAGRISSO arm compared to 4.2 months in the chemotherapy arm (HR 0.28; 95% CI: 0.20, 0.38).

*CNS Metastases Efficacy Data in AURA3*

A BICR assessment of CNS efficacy by RECIST 1.1 in the subgroup of 46/419 (11%) patients identified to have measurable CNS lesions on a baseline brain scan are summarized in Table 5.

**Table 5. CNS Efficacy by BICR in Patients with Measurable CNS Lesions at Baseline Brain Scan in AURA3**

| **Efficacy Parameter** | **TAGRISSO N=30** | **Chemotherapy N=16** |
|---|---|---|
| **CNS Objective Response Rate**[a,b] | | |
| CNS Objective Response Rate | 57% | 25% |
| (95% CI) | (37%, 75%) | (7%, 52%) |
| Complete response | 7% | 0% |
| Partial response | 50% | 25% |
| **CNS Duration of Response**[c] | | |
| Median Duration of Response, Months (Range) | NR (1.4, 12.5) | 5.7 (1.4, 5.7) |

NR Not Reached
[a] According to RECIST v1.1.
[b] Based on confirmed response.
[c] Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event.

*Pretreated T790M Positive NSCLC Patients – AURA Extension and AURA2*

The efficacy of TAGRISSO was demonstrated in two multicenter, single-arm, open-label clinical trials, AURA Extension and AURA2, in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. All patients were required to have EGFR T790M mutation-positive NSCLC as detected by the cobas® EGFR mutation test and received TAGRISSO 80 mg once daily. The major efficacy outcome measure of both trials was ORR according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Duration of response (DOR) and Progression-Free Survival (PFS) were additional outcome measures.

AURA Extension and AURA2 population characteristics were: median age 63 years (range 35 to 89), female (68%), White (36%), Asian (60%), never smoker (72%), World Health Organization (WHO) performance status 0 (37%) or 1 (63%), adenocarcinoma histology (96%), 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve] (31%), 2 or more prior lines of therapy (69%). Fifty-nine percent (59%) of patients had extra-thoracic visceral metastasis including 39% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases) and 29% with liver metastases. 47% of patients had metastatic bone disease. Somatic EGFR mutations in addition to T790M were exon 19 deletion (68%), L858R (29%), G719X (2%), and S768I (2%).

Efficacy results by BICR from AURA Extension and AURA2 are summarized in Table 6. The majority (96%) of patients with confirmed objective responses had ongoing responses ranging from 1.1 to

5.6 months after a median duration of follow-up of 4.2 months for AURA Extension and 4.0 months for AURA2.

**Table 6. Efficacy Results by BICR in AURA Extension and AURA2**

| Efficacy Parameter | Study 1 (N=201) | Study 2 (N=210) | Overall[2] (N=411) |
|---|---|---|---|
| Objective Response Rate[1] (95% CI) | 57% (50, 64) | 61% (54, 68) | 59% (54, 64) |
| Complete Response | 0 | 1% | 0.5% |
| Partial Response | 57% | 60% | 59% |

[1] Objective response rate according to RECIST v1.1.
[2] Pooled analysis of AURA Extension and AURA2.

In a separate dose finding part of AURA Extension, 63 patients with centrally confirmed T790M-positive NSCLC progressed on prior systemic therapy, including an EGFR TKI were administered TAGRISSO 80 mg. In these patients, the BICR-confirmed objective response rate was 51% (32/63) and the median duration of response was 12.4 months from the time of first documented response.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

80 mg tablets: beige, oval and biconvex tablet marked with "AZ 80" on one side and plain on the reverse and are available in bottles of 30 (NDC 0310-1350-30).

40 mg tablets: beige, round and biconvex tablet marked with "AZ 40" on one side and plain on the reverse and are available in bottles of 30 (NDC 0310-1349-30).

Store TAGRISSO bottles at 25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease/Pneumonitis
Inform patients of the risks of severe or fatal ILD, including pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.1)]*.

QTc Interval Prolongation
Inform patients of symptoms that may be indicative of significant QTc prolongation including dizziness, lightheadedness, and syncope. Advise patients to report these symptoms and to inform their physician about the use of any heart or blood pressure medications *[see Warnings and Precautions (5.2)]*.

- TAGRISSO can cause cardiomyopathy. Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Keratitis

- Advise patients to contact their healthcare provider immediately if they develop eye symptoms (eye inflammation, lacrimation, light sensitivity, eye pain, red eye or changes in vision) *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

- TAGRISSO can cause fetal harm if taken during pregnancy. Advise pregnant women of the potential risk to a fetus.
- Advise females to inform their healthcare provider if they become pregnant or if pregnancy is suspected, while taking TAGRISSO *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Females and Males of Reproductive Potential

- Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.3)]*.
- Advise males to use effective contraception during treatment and for 4 months after the final dose of TAGRISSO *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

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**Patient Information**
**TAGRISSO®** (tuh-GRISS-oh)
**(osimertinib)**
**tablets**

**What is the most important information I should know about TAGRISSO?**
**TAGRISSO may cause serious side effects, including:**

- **lung problems.** TAGRISSO may cause lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your doctor right away if you have any new or worsening lung symptoms, including trouble breathing, shortness of breath, cough, or fever.
- **heart problems, including heart failure.** TAGRISSO may cause heart problems that may lead to death. Your doctor should check your heart function before you start taking TAGRISSO and during treatment as needed. Tell your doctor right away if you have any of the following signs and symptoms of a heart problem: feeling like your heart is pounding or racing, shortness of breath, swelling of your ankles and feet, feeling lightheaded.
- **eye problems.** TAGRISSO may cause eye problems. Tell your doctor right away if you have symptoms of eye problems which may include watery eyes, sensitivity to light, eye pain, eye redness, or vision changes. Your doctor may send you to see an eye specialist (ophthalmologist) if you get eye problems with TAGRISSO.

See **"What are the possible side effects of TAGRISSO?"** for more information about side effects.

**What is TAGRISSO?**
TAGRISSO is a prescription medicine used to treat non-small cell lung cancer (NSCLC). TAGRISSO may be used when your non-small cell lung cancer has spread to other parts of the body and:

- has a certain type of abnormal epidermal growth factor receptor (EGFR) gene, called T790M, **and**
- you have had previous treatment with an EGFR tyrosine kinase inhibitor medicine and it has stopped working.

Your doctor will perform a test to make sure that TAGRISSO is right for you.
It is not known if TAGRISSO is safe and effective in children.

**Before taking TAGRISSO, tell your doctor about all of your medical conditions, including if you:**

- have lung or breathing problems.
- have heart problems, including a condition called long QTc syndrome.
- have problems with your electrolytes, such as sodium, potassium, calcium or magnesium.
- have a history of eye problems.
- are pregnant or plan to become pregnant. TAGRISSO can harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with TAGRISSO or think you may be pregnant.
  - **Females** who are able to become pregnant should use effective birth control during treatment with TAGRISSO and for 6 weeks after the final dose of TAGRISSO.
  - **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with TAGRISSO and for 4 months after the final dose of TAGRISSO.
- are breastfeeding or plan to breastfeed. It is not known if TAGRISSO passes into your breast milk. Do not breastfeed during treatment with TAGRISSO and for 2 weeks after your final dose of TAGRISSO. Talk to your doctor about the best way to feed your baby during this time.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements. Especially tell your doctor if you take a heart or blood pressure

medicine.

**How should I take TAGRISSO?**

- Take TAGRISSO exactly as your doctor tells you to take it.
- Your doctor may change your dose, temporarily stop, or permanently stop treatment with TAGRISSO if you have side effects.
- Take TAGRISSO 1 time each day.
- You can take TAGRISSO with or without food.
- If you miss a dose of TAGRISSO, do not make up for the missed dose. Take your next dose at your regular time.
- **If you cannot swallow TAGRISSO tablets whole:**
  - place your dose of TAGRISSO in a container that contains 60 mL (2 ounces) of water. Do not use carbonated water or any other liquids.
  - stir the TAGRISSO tablet and water until the TAGRISSO tablet is in small pieces (the tablet will not completely dissolve). Do not crush, heat, or use ultrasound to prepare the mixture.
  - drink the TAGRISSO and water mixture right away.
  - add 120 mL to 240 mL (4 to 8 ounces) of water into the container and drink to make sure that you take your full dose of TAGRISSO.

**What are the possible side effects of TAGRISSO?**

**TAGRISSO may cause serious side effects, including:**

See "**What is the most important information I should know about TAGRISSO?**"

**The most common side effects of TAGRISSO are:**

- diarrhea
- rash
- dry skin
- changes in your nails, including: redness, tenderness, pain, inflammation, brittleness, separation from nailbed, and shedding of nails
- tiredness

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of TAGRISSO. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store TAGRISSO?**

- Store TAGRISSO at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or that you no longer need.
- **Keep TAGRISSO and all medicines out of the reach of children.**

**General information about the safe and effective use of TAGRISSO.**

- Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TAGRISSO for a condition for which it was not prescribed. Do not give TAGRISSO to other people, even if they have the same symptoms you have. It may harm them. You can ask your doctor or pharmacist for information about TAGRISSO that is written for a healthcare professional.

**What are the ingredients in TAGRISSO?**

**Active ingredient:** osimertinib

**Inactive ingredients:** mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and sodium stearyl fumarate. Tablet coating contains: polyvinyl alcohol, titanium dioxide, macrogol 3350, talc,

ferric oxide yellow, ferric oxide red and ferric oxide black.

For more information, go to www.Tagrisso.com or call 1-800-236-9933.

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 2017