TAGRISSO® (osimertinib) tablets, for oral use

Initial U.S. Approval: 2015

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2.4 Dosage Modification

Adverse Reactions

Table 1. Recommended Dose Modifications for TAGRISSO

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

Other

Adverse reaction of Grade 3 or greater severity

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when coadministering with a strong CYP3A4 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), AUR2 (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 photophobia, 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:

Intestinal 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 AUR2 (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 20 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).

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Those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO. Of the 833 patients treated with TAGRISSO in clinical trials, 0.7% (n=6) of cases were fatal.

Conduct periodic monitoring with ECGs and electrolytes 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)].

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)].

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 photophobia, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

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)].
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

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

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) (N=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change from Baseline All Grades (%)</td>
<td>Change from Baseline to Grade 3 or Grade 4 (%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>61</td>
<td>75 (5.3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>63</td>
<td>61 (9.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46</td>
<td>48 (7.4)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27</td>
<td>49 (12)</td>
</tr>
</tbody>
</table>

* Based on the number of patients with available follow-up laboratory data

### 7.2 Effect of Osimertinib on Other Drugs

Coadministering TAGRISSO with a strong CYP3A4 inducer increased the exposure of osimertinib when administered to patients with EGFR mutations who are treated with TAGRISSO alone (see Clinical Pharmacology [12.3]). Increased osimertinib exposure may lead to reduced efficacy.

Avoid coadministration of TAGRISSO with strong CYP3A4 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 CYP3A4 inducers.

### 7 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 end of organogenesis (gestation days 5-20) at a dose of 80 mg/kg/day, which produced plasma exposures of 80 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death.

### 8.2 Lactation

**Risk Summary**

There are no data on the presence of osimertinib in human milk, the effects of osimertinib on the breastfeeding 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.
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 (PCS; 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 (Cmax) 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 pharmacokinetic analysis (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 Cmax to Cmin (minimal concentration) ratio was 1.8-fold.

Absorption

The median time to Cmax 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 Cmax and AUC of osimertinib were comparable to that under fasting conditions.

Distribution

The mean volume of distribution at steady-state (Vd/F) of osimertinib was 997 L. Plasma protein binding of osimertinib is likely high based on its physiochemical properties.

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: Coadministration TAGRISSO with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure to osimertinib (AUC increased by 24% and Cmax 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 rosvustatin (a BCRP substrate) increased rosuvastatin AUC by 35% and Cmax 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 Vivo 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 0.3-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 anestrous, 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 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/m2 with carboplatin AUC5 or pemetrexed 500mg/m2 with cisplatin 75 mg/m2 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/m2 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 (BIRC) 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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>TAGRISSO (N=279)</th>
<th>Chemotherapy (N=140)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>140 (50)</td>
<td>110 (79)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>129 (46)</td>
<td>104 (74)</td>
</tr>
<tr>
<td>Death</td>
<td>11 (4)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Median PFS in months (95% CI)</td>
<td>10.1 (8.3, 12.3)</td>
<td>4.4 (4.2, 5.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.30 (0.23,0.41)</td>
<td></td>
</tr>
<tr>
<td>P-value *</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Objective Response Rate</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rate</td>
<td>65%</td>
<td>29%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(59%, 70%)</td>
<td>(21%, 37%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Partial response</td>
<td>63%</td>
<td>27%</td>
</tr>
<tr>
<td>P-value *</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Duration of Response (DoR)</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Duration of Response in months (95% CI)</td>
<td>11.0 (8.6, 12.6)</td>
<td>4.2 (3.0, 5.9)</td>
</tr>
</tbody>
</table>

* Without documented radiological disease progression
  * Stratified by ethnicity (Asian vs. non-Asian)
  * Pike estimator
  * Stratified log-rank test
  * Confirmed
  * 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.
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, (72%), World Health Organization (WHO) performance status 0 (37%) or 1 (63%), adenocarcinoma histology (96%), 1 prior line of therapy [EGFR-TKI treatment only, 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 (88%), 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

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>Study 1 (N=201)</th>
<th>Study 2 (N=210)</th>
<th>Overalla (N=411)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response Rateb (95% CI)</td>
<td>57% (90, 64)</td>
<td>61% (54, 68)</td>
<td>59% (54, 64)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>0%</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>57%</td>
<td>60%</td>
<td>59%</td>
</tr>
</tbody>
</table>

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.
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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