TAGRISSO™

osimertinib mesilate

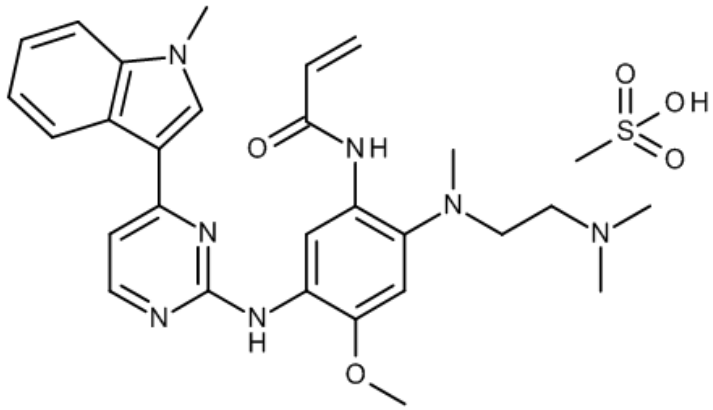
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in TAGRISSO is osimertinib mesilate.

The chemical name of osimertinib mesilate is: N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesilate salt

The chemical structure of osimertinib mesilate is:



Molecular formula: $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$

Molecular weight: 595.71

CAS number: 1421373-66-1

DESCRIPTION

Osimertinib mesilate is a single crystalline form solid, which is slightly soluble in water (3.1 mg/mL at 37°C) and has pKa values of 9.5 (aliphatic amine) and 4.4 (aniline).

There are 2 strengths of TAGRISSO film-coated tablets containing either 40 mg or 80 mg of osimertinib as the mesilate salt. Both strengths also contain mannitol, microcrystalline cellulose, hyprolose, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, talc, iron oxide black, iron oxide red, iron oxide yellow and macrogol 3350.

The 40 mg tablets are round, biconvex, beige, film-coated tablets with a diameter of approximately 9 mm. The tablets are debossed with 'AZ' over '40' on 1 side and plain on the reverse.

The 80 mg tablets are oval, biconvex, beige, film-coated tablets measuring approximately 7.25 × 14.5 mm. The tablets are debossed with 'AZ 80' on 1 side and plain on the reverse.

PHARMACOLOGY

Osimertinib is an orally administered Tyrosine Kinase Inhibitor (TKI). It is a selective and irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations.

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 IC_{50}s from 6 nM to 54 nM against phospho-EGFR) (see also Metabolism). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC_{50}s 480 nM to 1.8 μM against phospho-EGFR). In vivo oral administration of osimertinib leads to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models. Osimertinib also showed significant anti-tumour activity, associated with increased survival, in a mouse brain xenograft metastasis model (PC9; exon 19 del).

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 significant efficacy relationship (objective response rate (ORR), Duration of Response (DoR) and Progression-Free Survival (PFS)) for osimertinib was identified. Over the same dose range, increased exposure led to increased probability of adverse reactions, specifically rash, diarrhoea and ILD.

Pharmacokinetics

Osimertinib pharmacokinetic parameters have been characterized in healthy subjects and NSCLC patients. Based on population PK analysis, osimertinib apparent plasma clearance is 14.2 L/h, apparent volume of distribution is 997 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

In a relative bioavailability study against an oral solution of osimertinib mesilate, both TAGRISSO and the oral solution produced peak plasma concentrations of osimertinib with median (min-max) t_{max} of 6 (3 - 24) hours, with several peaks

observed over the first 24 hours in some patients. The AUC and C_{max} values for TAGRISSO and the oral solution were also similar, indicating similar relative bioavailability. The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73). A food effect study conducted with a 20 mg dose of TAGRISSO tablets showed minimal effect on C_{max} and AUC (14% and 19%, increased with a high fat, high calorie meal). In the AURAex and AURA2 studies (see CLINICAL TRIALS), patients were instructed to take TAGRISSO when fasted. 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 with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

Population estimated mean volume of distribution at steady state (Vss/F) of osimertinib is 997 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. Penetration of the blood-brain barrier by osimertinib has been demonstrated in the mouse, rat and cynomolgus monkey, with exposure in the brain approximately 2–3 times higher than for blood (based on Cmax or AUC).

Metabolism

In vitro studies indicate that osimertinib is metabolised predominantly by CYP3A4 and CYP3A5. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in plasma after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to osimertinib while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of osimertinib to patients, with a median (min-max) t_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In a pharmacokinetic and mass balance study of orally administered radio-labelled osimertinib mesilate, 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 remaining 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. Minor glutathione, cysteinylglycine, glucuronide and sulphate conjugates were also observed in rat and dog in vitro. 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, 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.

Transporter interactions

In vitro studies have shown that osimertinib is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate of the hepatocyte uptake transporters OATP1B1 and OATP1B3.

In vitro, osimertinib does not inhibit P-glycoprotein, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2-K and OCT2 at clinically relevant concentrations, but does inhibit BCRP.

Special populations

In a population based pharmacokinetic analyses, no clinically significant relationships were identified between predicted steady state exposure (AUC_{ss}) and patient's age, gender, ethnicity and smoking status. Population PK analysis indicated that body weight and serum albumin were significant covariates but the exposure changes due to body weight or baseline albumin 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. Clinical studies that were conducted excluded patients with AST or ALT >2.5 x upper limit of normal (ULN), or if due to underlying malignancy, >5.0 x ULN or with total bilirubin >1.5 x ULN. Based on a pharmacokinetic analysis of 104 patients with mild hepatic impairment (total bilirubin ≤ ULN and AST between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST), 8 patients with moderate hepatic impairment (total bilirubin between 1.5 times to 3.0 times ULN and any AST) and 972 patients with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN), osimertinib exposures were similar. There are limited data available on patients with severe hepatic impairment.

Renal Impairment

A pharmacokinetic study in patients with renal impairment has not been conducted. Based on a population pharmacokinetic analysis of 471 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 208 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min), 5 patients with severe renal impairment (CLcr 15 to less than 30 mL/min) and 402 patients with normal renal function (greater than or equal to 90 mL/min), osimertinib exposures

were similar. In this analysis, data from patients with severe renal impairment (n = 5), is very limited (see also DOSAGE AND ADMINISTRATION – Renal Impairment). Patients with CLcr less than 15 mL/min were not included in the clinical trials.

Cardiac electrophysiology

The QT interval prolongation potential of osimertinib 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 QT intervals (see PRECAUTIONS – QT interval prolongation). A pharmacokinetic analysis with osimertinib predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

CLINICAL TRIALS

T790M Positive Advanced NSCLC

TAGRISSO has not been studied in previously untreated patients with EGFR T790M mutation positive NSCLC.

Pretreated T790M positive NSCLC patients-AURA3

The efficacy and safety of TAGRISSO for the treatment of patients with locally advanced or metastatic T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomized, open label, active-controlled Phase 3 study (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. The T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy outcome was progression-free survival (PFS) as assessed by investigator. Additional efficacy outcome measures included Objective Response Rate (ORR), Duration of Response (DoR) and overall survival (OS) as assessed by investigator.

Patients were randomized in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomization was stratified by ethnicity (Asian and non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500mg/m^2 with carboplatin AUC5 or pemetrexed 500mg/m^2 with cisplatin 75mg/m^2) on Day 1 of every 21d cycle for up to 6 cycles. Patients whose disease has not progressed after four cycles of platinum-based chemotherapy may receive pemetrexed maintenance therapy (pemetrexed 500mg/m^2 on Day 1 of every 21d cycle). Subjects on the chemotherapy arm who had objective radiological progression (by the investigator and confirmed by independent central imaging review) were given the opportunity to begin treatment with TAGRISSO.

The baseline demographic and disease characteristics of the overall study population were: median age 62 years, 15% of patients were ≥75 years old, female (64%), White (32%), Asian (65%). Sixty-eight percent (68%) of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy as assessed by investigator (refer Table 1 and Figure 1)

Table 1. Efficacy results from AURA3 by investigator assessment

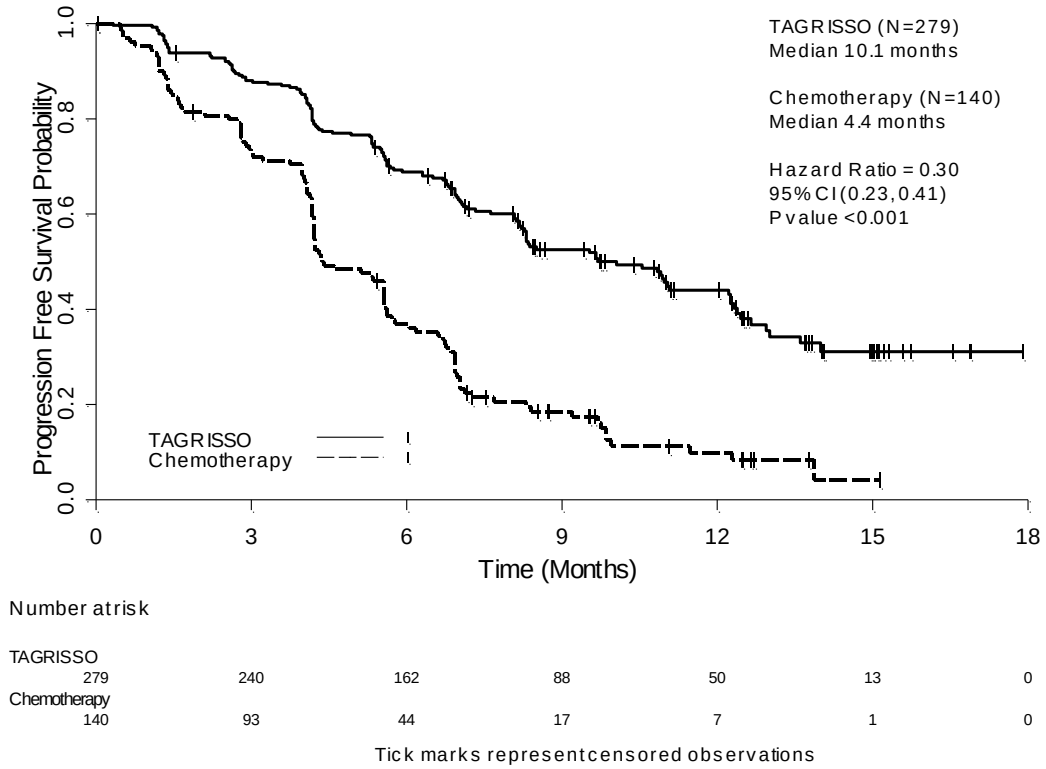
Efficacy Parameter	**TAGRISSO (N=279)**	**Chemotherapy (N=140)**
Progression-Free Survival		
Number of Events (% maturity)	140 (50)	110 (79)
Median, Months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
HR (95% CI) ; P-value	0.30 (0.23,0.41) ; P value < 0.001	
Objective Response Rate		
Number of responses, Response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Complete Response	1%	1%
Partial Response	69%	30%
Odds ratio (95% CI) ; P-value	5.4 (3.5, 8.5); P value <0.001	
Duration of Response (DoR)		
Median, Months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

HR=Hazard Ratio; CI=confidence interval

All efficacy results based on RECIST investigator assessment

A HR< 1 favours TAGRISSO

Figure 1. Kaplan-Meier Curves of Progression-Free Survival as assessed by investigator in AURA3



A sensitivity analysis of PFS was conducted by a Blinded Independent Central Review (BICR) and showed a median PFS of 11.0 months with TAGRISSO compared with 4.2 months with chemotherapy. This analysis demonstrated a consistent treatment effect (HR 0.28; 95% CI: 0.20, 0.38) with that observed by investigator assessment.

Clinically meaningful improvements in PFS with HRs less than 0.50 in favour of patients receiving TAGRISSO compared to those receiving chemotherapy were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, CNS metastases status at study entry, EGFR mutation (Exon 19 deletion and L858R), and duration of first-line therapy with an EGFR-TKI. The study was not powered for these subgroup analyses.

CNS metastasis efficacy data in AURA3 study

A BICR assessment of CNS efficacy by RECIST v1.1 in patients identified to have CNS metastases on a baseline brain scan are summarized in Table 2.

Table 2. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

Efficacy Parameter	TAGRISSO N=30	Chemotherapy N=16
CNS Objective Response Rate[1]		
CNS response rate % (n/N) (95% CI)	57% (37%, 75%)	25% (7%, 52%)
Complete Response	7%	0%
Partial response	50%	25%
CNS Duration of Response[2]		
Median, Months (95% CI)	NC (6.0, NC)	5.7 (NC, NC)
CNS Progression-free survival[3]	N=75	N=41
Number of Events (% maturity)	19 (25)	16 (39)
Median, Months (95% CI)	11.7 (10, NC)	5.6 (4.2, 9.7)
HR (95% CI); P value	0.32 (0.15, 0.69); 0.004	

[1] CNS Objective Response Rate and Duration of Response determined by RECIST v1.1 by CNS BICR in the evaluable for response population (CNS measurable lesions at baseline by BICR) n=30 for TAGRISSO and n=16 for Chemotherapy

[2] Based on patients in the evaluable for response population with confirmed response only; DoR defined as the time from the date of first documented response (complete response or partial response, or stable disease ≥6 weeks)

[3] CNS Progression Free Survival determined by RECIST v1.1 by CNS BICR in the full analysis set population (CNS measurable and non-measurable lesions at baseline by BICR) n=75 for TAGRISSO and n=41 for Chemotherapy

NC=non-calculable;

A HR <1 favours TAGRISSO

Pretreated T790M positive NSCLC patients-AURAex and AURA2

Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation-positive lung cancer who have progressed on one or more prior systemic therapy, including an EGFR TKI. 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 dosing. T790M mutation status was also assessed retrospectively using ctDNA extracted from a plasma sample taken during screening. 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 Committee (BICR). Secondary efficacy outcome measures included Duration of Response (DoR) 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, second line, chemotherapy naïve), 69% (N=282) had received 2 or more prior lines. Seventy-two percent of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. 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. Forty-seven percent (47%) of patients had metastatic bone disease. The median duration of follow up for PFS was 12.6 months.

In the 411 pre-treated EGFR T790M mutation positive patients, the ORR by Blinded Independent Central Review (BICR) in the evaluable for response population was 66% (95% CI: 61, 71). In patients with a confirmed response by BICR, the median DoR was 12.5 months (95% CI: 11.1, NE). The median PFS by BICR was 11.0 months 95% CI (9.6, 12.4).

Overall response rates by BCIR above 50% were observed in all predefined subgroups analysed, including line of therapy, race, age and region. The ORR by BICR in AURAex was 62% (95% CI: 55, 68) and 70% (95% CI: 63, 77) in AURA2.

In the evaluable for response population with objective responses, 85% (223/262) had documentation of response at the time of the first scan (6 weeks); 94% (247/262) had documentation of response at the time of the second scan (12 weeks).

CNS metastases efficacy data in Phase 2 studies (AURAex and AURA2)

A BICR assessment of CNS efficacy by RECIST v1.1 was performed in a subgroup of 50 (out of 411) patients identified to have measurable CNS metastases on a baseline brain scan. A CNS ORR of 54% (27/50 patients; 95% CI: 39.3, 68.2) was observed with 12% being complete responses.

INDICATIONS

TAGRISSO is indicated for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer.

CONTRAINDICATIONS

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

PRECAUTIONS

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 for all patients. A validated test should be performed in a clinical laboratory using either tumour tissue DNA or circulating tumour DNA (ctDNA) obtained from a blood (plasma) sample.

Only robust, reliable and sensitive test(s) with demonstrated utility for the determination of EGFR mutation status should be used (see CLINICAL TRIALS).

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.

The pooled clinical safety data described below under precautions reflect exposure to TAGRISSO in 833 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy.

Interstitial Lung Disease (ILD)

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.5% and were fatal in 0.6% (n=5) of the 833 patients who received osimertinibin AURA studies. Most cases improved or resolved with discontinuation 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.

The incidence of ILD was 8.2% in patients of Japanese ethnicity, 1.9% in patients of non-Japanese Asian ethnicity and 2.9% in non-Asian patients.

Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms indicative of ILD (e.g dyspnoea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed.

TAGRISSO is not approved for use in combination with PD1/PDL1 checkpoint inhibitors. In an uncontrolled phase 1 study, an increased incidence of pneumonitis was observed in the combination of osimertinib with a PDL1 checkpoint inhibitor.

QT Interval Prolongation

QTc interval prolongation occurs in patients treated with TAGRISSO. Of the 833 patients in AURA studies treated with TAGRISSO 80 mg, 0.7% of patients (n = 6) were found to have a QTc greater than 500 msec, and 2.9% pf patients (n = 24) had an increase from baseline QTc greater than 60 msec. 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.

A pharmacokinetic analysis with TAGRISSO at 80 mg in AURA2 predicted a drug-related QTc interval prolongation of 14 msec with an upper bound of 16 msec (90% CI). No QTc-related arrhythmias were reported in the AURA studies.

When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome. Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold TAGRISSO 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 6. Permanently discontinue TAGRISSO 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.

Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, a causal relationship between effects on changes in cardiac contractility and TAGRISSO has not been established. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Keratitis

Keratitis was reported in 0.7% (n=6) of the 833 patients treated with TAGRISSO in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist (see ADVERSE EFFECTS).

Effects on 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. Due to the potential for effects on egg and sperm development women should not conceive and men should not father a child while receiving TAGRISSO.

Based on studies in animals, male and female fertility may be impaired by treatment with TAGRISSO. Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for ≥ 4 weeks and there was a reduction in male fertility in rats following exposure to osimertinib for ~2.5 months. These findings were seen at exposure similar to the clinical exposure at 80 mg daily (based on AUC). Pathology findings in the testes seen in rats following 4 weeks dosing were reversible.

In a female fertility study in rats, oral administration of TAGRISSO at 20 mg/kg/day (approximately equal to exposure in humans at the recommended daily clinical dose of 80 mg) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility following a 1 month treatment-free period. 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 ≥ 4 weeks at 10 mg/kg/day (total exposure 0.3 times the clinical exposure). Findings in the ovaries seen following 4 weeks dosing were reversible.

Use in pregnancy – Category D

There are no adequate and well-controlled studies in pregnant women using TAGRISSO. Based on its mechanism of action and preclinical data, osimertinib may cause foetal harm when administered to a pregnant woman. If TAGRISSO is used during pregnancy or if the patient becomes pregnant while receiving TAGRISSO, she should be informed of the potential hazard to the foetus or potential risk for miscarriage.

Due to the risk of foetal harm, women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception and continue to use the contraception for the following periods after completion of treatment with TAGRISSO: at least 6 weeks in female patients and longer in male patients (4 months). A risk for decreased exposure of hormonal contraceptives cannot be excluded (see Interactions – Active substances whose plasma concentrations may be altered by TAGRISSO).

In a modified embryofoetal development study in the rat, osimertinib caused embryolethality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg/day 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. Teratogenicity has not been adequately assessed in animal studies. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable excretion in milk and 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).

Use in lactation

It is not known whether osimertinib or its metabolites are present in human milk. When osimertinib was administered to lactating rats, osimertinib and its metabolites were detected in the suckling pups and there were adverse effects on pup growth and survival. Due to potential for transfer through breast milk, breast-feeding mothers are advised to discontinue breast-feeding infants while receiving TAGRISSO therapy.

Carcinogenicity

Carcinogenicity studies have not been performed with osimertinib.

Genotoxicity

Osimertinib showed no activity in in vitro bacterial and mouse lymphoma cell mutation assays and in in vivo rat bone marrow micronucleus assays, suggesting that it is neither a mutagen nor a clastogen.

INTERACTIONS WITH OTHER MEDICINES

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 1 metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, TAGRISSO co-administered 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 Cmax decreased 20%. Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib.

Active substances that may decrease osimertinib plasma concentrations

In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced 78% when co-administered with rifampicin (600 mg daily for 21 days). It is recommended that concomitant use of strong CYP3A inducers (e.g. phenytoin, rifampicin, carbamazepine, St John’s Wort) with TAGRISSO should be avoided. If not possible, then increase TAGRISSO dose to 160 mg during the treatment with strong CYP3A inducer and resume at 80 mg, 3 weeks after discontinuation of the strong CYP3A inducer.

Based on physiologically-based pharmacokinetic (PBPK) model simulations, no dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

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 transporter.

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

In a clinical PK study, co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and Cmax of simvastatin by 9% and 23% respectively. These changes are small and not likely to be of clinical significance. Clinical pharmacokinetic 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. Patients taking concomitant medications where the disposition is dependent upon CYP1A2, CYP2C or P-glycoprotein and with narrow therapeutic index should be closely monitored for reduction in therapeutic activity of the concomitant medication as a result of reduced exposure whilst receiving TAGRISSO.

Driving and operating machinery

No studies on the effects on the ability to drive and use machines have been performed. If patients experience symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

ADVERSE EFFECTS

Studies in EGFR T790M mutation positive NSCLC patients previously treated with an EGFR TKI

The data described below reflect exposure to TAGRISSO in 690 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy. These patients received TAGRISSO at a dose of 80 mg daily in one randomized Phase 3 study (AURA3-second line only) and 2 single-arm studies (AURAex and AURA2-second line or greater) (see CLINICAL TRIALS). In AURA3, the median duration of study treatment was 8.1 months for patients in the TAGRISSO arm (n=279) and 4.2 months for patients in the chemotherapy arm (n=136). The majority of patients in the pooled Phase 2 studies were heavily pre-treated: 68% had received at least 2 prior treatment regimens and 46% had received 3 or more prior lines of therapy. In addition to EGFR-TKI therapy, approximately two third (63%) of patients had received prior platinum based chemotherapy. The overall median duration of study treatment in AURAex and AURA2 was 13 months (n=411).

Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (44%) and rash (41%). Grade 3 and grade 4 adverse events with TAGRISSO were 26% and 2.0%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 2.3% of the patients.

Discontinuation due to adverse reactions or abnormal laboratory parameters was 6.5%.

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. 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. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

Adverse reactions have been assigned to the frequency categories in Table 4 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the 690 previously treated EGFR T790M mutation positive patients who received TAGRISSO at a dose of 80 mg daily in the AURA3, AURAex and AURA2 studies.

Adverse reactions are listed according to system organ class in MedDRA. The corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: very common (≥1/10); common (>1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from available data). Table 4 summarises the adverse reactions from AURAex (Phase 2), AURA2 and AURA3 studies for patients receiving at least one dose of TAGRISSO.

Table 4. Adverse Reactions Reported in AURA[a] studies

MedDRA SOC	MedDRA Term	CIOMS descriptor/ Overall Frequency (all CTCAE grades[b])	Frequency of CTCAE grade 3 or higher
Gastrointestinal disorders	Diarrhoea	Very common (44%)	1.0%
	Stomatitis	Very common (15%)	0%
Eye disorders	Keratitis[g]	Uncommon (0.9%)	0%
Skin and subcutaneous tissue disorders	Rash[c,]	Very common (41%)	0.7%
	Dry Skin[d]	Very common (29%)	0%
	Paronychia[h]	Very common (27%)	0%
	Pruritus[i]	Very common (15%)	0%
Respiratory, thoracic and mediastinal disorders	Interstitial Lung Disease[e]	Common (3.2%) 0.6% of cases reported in patients taking TAGRISSO were fatal	1.3%

Investigations	QTc interval prolongation[j]	Uncommon (0.7%)	
Findings based on test results presented as CTCAE grade shifts	Platelet count decreased[f]	Very common (54%)	2.1%
	Leukocytes decreased[f]	Very common (66%)	2.4%
	Neutrophils decreased[f]	Very common (32%)	4.3%

[a] Data is cumulative from Phase 3 (AURA3) and Phase 2 (AURAex 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 for rash AEs: Rash, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash vesicular, rash follicular, acne pustular, rash pustular, folliculitis, eyelid folliculitis, acne, dermatitis acneiform, and drug eruption.

[d] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, and eczema.

[e] Includes cases reported within the clustered terms: Interstitial lung disease, lung disorder, pneumonitis, diffuse alveolar damage, pulmonary fibrosis, alveolitis, idiopathic pulmonary fibrosis, acute interstitial pneumonitis, and pulmonary toxicity.

[f] Represents the incidence of laboratory findings, not of reported adverse events.

[g] Includes cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect, corneal defect.

[h] Includes cases reported within the clustered terms: Nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.

[i] Includes cases reported within the clustered terms: Pruritus, pruritus generalised, eyelid pruritus.

j Represents the incidence of patients who had a QTcF prolongation >500msec.

Description of selected adverse reactions

The pooled clinical safety data described in this section reflect exposure to TAGRISSO in 833 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy.

Interstitial lung disease (ILD

In the AURA studies, the incidence of ILD was 8.2% in patients of Japanese ethnicity, 1.9% in patients of non-Japanese Asian ethnicity and 2.9% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.7 months (see PRECAUTIONS).

QT Interval Prolongation

Of the 833 patients in AURA studies treated with TAGRISSO 80 mg, 0.7% of patients (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. A pharmacokinetic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the AURA studies (see PRECAUTIONS).

Cardiac Contractility

Left Ventricular Ejection Fraction (LVEF) Analysis

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment (see PRECAUTIONS).

Cardiac adverse events

In the Phase II studies 5 patients (1.2%) were reported to have 6 adverse events consistent with cardiac failure or cardiomyopathy. The reported adverse events were; Congestive heart failure (2 events in 1 patient with fatal outcome; 0.2%), ejection fraction decreased (3 events; 0.7%) and pulmonary oedema (1 event; 0.2%).

Table 5. ADRs in AURA3 study

MedDRA SOC	**TAGRISSO overall frequency (N=279)**		**Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)**	
NCI Grade	**Any Grade (%)**	**Grade 3 or higher (%)**	**Any Grade (%)**	**Grade 3 or higher (%)**
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Interstitial Lung Disease[c,d]	3.6	0.4	0.7	0.7
Eye disorders				
Keratitis[e]	1.1	0	0.7	0
Gastrointestinal disorders				
Diarrhoea	41	1.1	11	1.5
Stomatitis	15	0	15	1.5

Skin and subcutaneous tissue disorders				
Rash[f]	34	0.7	5.9	0
Dry skin[g]	23	0	4.4	0
Paronychia[h]	22	0	1.5	0
Pruritus[i]	13	0	5.1	0
Investigations QTc interval prolongation[j]	1.4		0	
(Findings based on test results presented as CTCAE grade shifts)				
Platelet count decreased[k]	46	0.7	48	7.4
Leukocytes decreased[k]	61	1.1	75	5.3
Neutrophils decreased[k]	27	2.2	49	12

[a] Data is cumulative from AURA3 study; 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] 1 CTCAE grade 5 event (fatal) was reported.

[e] Includes cases reported within the clustered terms: keratitis, punctate keratitis, corneal epithelium defect and corneal erosion.

[f] 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.

[g] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema.

[h] Includes cases reported within the clustered terms: Nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.

[i] Includes cases reported within the clustered terms: Pruritus, pruritus generalised, eyelid pruritus.

[j] Represents the incidence of patients who had a QTcF prolongation >500msec

[k] Represents the incidence of laboratory findings, not of reported adverse events.

Safety findings in the single-arm Phase 2 AURAex and AURA2 studies were generally consistent with those observed in the AURA3 TAGRISSO arm. No additional or unexpected toxicity has been observed and adverse events have been aligned in type, severity and frequency.

Special populations

Elderly

In AURA3 (n = 279), 41% of patients were 65 years of age and older, of whom 15% were 75 years of age and older. Compared with younger subjects (< 65),

more subjects ≥ 65 years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (5.3% versus 4.2%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (5.3% versus 2.4%). No overall differences in efficacy were observed between these subjects and younger subjects. A consistent pattern in safety and efficacy results was observed in the analysis of AURA Phase 2 studies.

DOSAGE AND 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 CLINICAL TRIALS).

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.

T790M mutation status may be first assessed using a plasma-based ctDNA test, but if results are negative then sampling of tumour tissue should be attempted whenever feasible. Positive determination of T790M mutation status by either a plasma-based or tissue-based test indicates the patient is eligible for treatment with TAGRISSO.

Dosage in adults

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

TAGRISSO can be taken without regard to food at the same time each day.

The tablets should be swallowed whole with water. The tablet should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, it may first be dispersed in 50 mL of non-carbonated water. The tablet 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.

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 nasogastric 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.

Missed dose

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

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 of TAGRISSO should be reduced to 40 mg taken once daily. Dose reduction guidelines for adverse reactions toxicities are provided in Table 6.

Table 6. Dose adjustment information for adverse reactions

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue treatment
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold treatment 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 treatment
Other	Grade 3 or higher adverse reaction	Withhold treatment for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of treatment for up to 3 weeks	Treatment 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 treatment

[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.

Special patient populations

No dosage adjustment is required according to patient age, body weight, gender, ethnicity and smoking status.

Paediatric and Adolescents

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

Elderly (>65 years)

Population PK analysis indicated that age did not have an impact on the exposure of osimertinib and hence, TAGRISSO can be used in adults without regard to age.

Hepatic impairment

No clinical studies have been conducted to specifically evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild or moderate hepatic impairment. The appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment. Until additional data become available, use of TAGRISSO in patients with severe hepatic impairment is not recommended.

Renal Impairment

No clinical study has been conducted to specifically evaluate the effect of renal impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild, moderate or severe renal impairment; there are very limited data in patients with severe renal impairment (n=5). As patients with CLcr less than 15 mL/min or on dialysis were not included in the clinical trials, caution should be exercised when treating these patients.

OVERDOSAGE

In TAGRISSO clinical trials a limited number of patients were treated with 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, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management.

PRESENTATION AND STORAGE CONDITIONS

The 40 mg tablets are round, biconvex, beige, film-coated tablets with a diameter of approximately 9 mm. The tablets are debossed with ‘AZ’ over ‘40’ on 1 side and plain on the reverse.

The 80 mg tablets are oval, biconvex, beige, film-coated tablets measuring approximately 7.25 × 14.5 mm. The tablets are debossed with ‘AZ 80’ on 1 side and plain on the reverse.

The tablets are packed into PVC/aluminium/polyamide laminate blister strips in cartons of 30 tablets.

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

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MACQUARIE PARK NSW 2113

Telephone: 1800 805342

POISON SCHEDULE OF THE MEDICINE

Schedule 4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

3rd August 2016

DATE OF MOST RECENT AMENDMENT

10 May 2018