PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

TAGRISSO® 40 mg Film-coated tablets

TAGRISSO® 80 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TAGRISSO 40 mg: Each film-coated tablet contains 40 mg osimertinib (as osimertinib mesylate).

TAGRISSO 80 mg: Each film-coated tablet contains 80 mg osimertinib (as osimertinib mesylate).

Sugar-free

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

TAGRISSO 40 mg: Film-coated tablet, beige, 9 mm, round, biconvex tablet, debossed with “AZ” and “40” on one side and plain on the reverse.

TAGRISSO 80 mg: Film-coated tablet, beige, 7.25 x 14.5 mm, oval, biconvex tablet debossed with “AZ” and “80” on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TAGRISSO is indicated for:

- The adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (see section 5.1).
- The first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

- The treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC predominantly bronchial adenocarcinoma whose disease has progressed on or after EGFR TKI therapy.

4.2 Posology and method of administration

Posology

The recommended dose of TAGRISSO is 80 mg once a day.

Patients in the adjuvant setting should receive treatment until disease recurrence or unacceptable toxicity. Treatment duration for more than 3 years was not studied.

Patients with locally advanced or metastatic lung cancer should receive treatment until disease progression or unacceptable toxicity.

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

When considering the use of TAGRISSO, EGFR mutation status (in tumour specimens for adjuvant treatment and tumour or plasma specimens for locally advanced or metastatic setting) should be determined using a validated test method (see section 4.4) for:

- exon 19 deletions or exon 21 (L858R) substitution mutations (for first-line treatment).
- T790M mutations (following progression on or after EGFR TKI therapy).

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

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

Dose adjustments

Dosing interruption and/or dose reduction may be required based on individual safety and tolerability.

If dose reduction is necessary, then the dose of TAGRISSO should be reduced to 40 mg taken once daily.

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

Table 1. Recommended dose modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	ILD/Pneumonitis	Permanently discontinue TAGRISSO
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue TAGRISSO
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO
[a]Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.		

Special patient populations

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

Paediatric and adolescents

The safety and efficacy of TAGRISSO in children or adolescents aged less than 18 years have not

been established. No data is available.

Hepatic impairment

Based on clinical studies, no dose adjustments are necessary in patients with mild hepatic impairment (Child Pugh Class A) or moderate hepatic impairment (Child Pugh Class B).13 Similarly, based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1,0 to 0,5x ULN and any AST) 1or moderate hepatic impairment (total bilirubin between 1,5 to 3 times ULN and any AST). The appropriate dose of TAGRISSO has not been established in patients with severe hepatic impairment (see section 5.2).

Renal impairment

No clinical studies have been conducted to specifically evaluate the effect of renal impairment on the pharmacokinetics of TAGRISSO. No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. The safety and efficacy of TAGRISSO has not been established in patients with end-stage renal disease [Creatinine clearance (CLcr) less than 15 ml/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with end-stage renal impairment (see section 5.2).

Elderly (>65 years)

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

Method of administration

TAGRISSO is for oral use. The tablet 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. No other liquids should be added.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- St. John's Wort should not be used with TAGRISSO (see section 4.5).
- Pregnancy and Lactation (see section 4.6).

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of TAGRISSO as adjuvant treatment after complete tumour resection in patients with NSCLC, it is important that the EGFR mutation positive status (exon 19 deletions (Ex19del) or exon 21 L858R substitution mutations (L858R)) indicates treatment eligibility. A validated test should be performed in a clinical laboratory using tumour tissue DNA from biopsy or surgical specimen.

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

Positive determination of EGFR mutation status (exon 19 deletions or exon 21 (L858R) substitution mutations for first-line treatment or T790M mutations following progression on or after EGFR TKI therapy) (activating EGFR mutations for first-line treatment or T790M mutations following progression on or after EGFR TKI therapy) 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.

Only robust, reliable and sensitive tests with demonstrated utility for the determination of EGFR mutation status should be used.

Interstitial lung disease (ILD)

ILD or ILD-like adverse reactions were reported in 3,7 % of the 1 479 patients who received TAGRISSO in the ADAURA, FLAURA and AURA studies. Five fatal cases were reported in the locally advanced or metastatic setting. No fatal cases were reported in the adjuvant setting. The incidence of ILD was 10,9 % in patients of Japanese ethnicity, 1,6 % in patients of non-Japanese Asian ethnicity and 2,5 % in non-Asian patients.

The median time to onset of ILD or ILD-like adverse reactions was 2,7 months. Withhold TAGRISSO and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e.g. dyspnoea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed.

QTc Interval Prolongation

When possible, avoid use of TAGRISSO in patients with congenital long QT syndrome (see section 4.8). Consider periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicines 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 1.

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 dysrhythmia.

Changes in cardiac contractility

Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 3,9 % and a drop to less than 50 % occurred in 3,2 % (40/1233) 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. In an adjuvant placebo-controlled trial (ADAURA), 1,6 % (5/312) of patients treated with TAGRISSO and 1,5 % (5/331) of patients treated with placebo experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50 %.

Keratitis

Keratitis was reported in 0,7 % (n=10) of the 1 479 patients treated with TAGRISSO in the ADAURA, FLAURA and 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 section 4.2).

Stevens-Johnson Syndrome

Case reports of Stevens-Johnson syndrome (SJS) have been reported rarely in association with TAGRISSO treatment. Before initiating treatment, patients should be advised of signs and symptoms of SJS. If signs and symptoms suggestive of SJS appear, TAGRISSO should be interrupted or discontinued immediately.

4.5 Interaction with other medicines and other forms of interaction

Strong CYP3A4 inducers can decrease the exposure of TAGRISSO. TAGRISSO may increase the exposure of breast cancer resistant protein (BCRP) and P-glycoprotein (P-gp) substrates.

Active substances that may increase TAGRISSO plasma concentrations

The Phase I metabolism of TAGRISSO is predominantly via CYP3A4 and CYP3A5. 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 % (90 % CI 15; 35) and Cmax decreased -20 % (90 % CI -27; -13). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of TAGRISSO.

Active substances that may decrease TAGRISSO plasma concentrations

No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers. TAGRISSO should be avoided with strong CYP3A inducers (see section 5.2).

Effect of gastric acid reducing active substances on TAGRISSO

Co-administration of omeprazole did not result in clinically relevant changes in TAGRISSO exposures. Gastric pH modifying medicines can be concomitantly used with TAGRISSO without any restrictions.

Active substances whose plasma concentrations may be altered by TAGRISSO

TAGRISSO is a competitive inhibitor of BCRP transporter. Co-administration of TAGRISSO with rosuvastatin (sensitive BCRP substrate) increased the AUC and Cmax of rosuvastatin by 35 % (90 % CI 15, 57) and 72 % (90 % CI 46, 103), respectively. Patients taking concomitant medicines with disposition 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 medicines whilst receiving TAGRISSO. Co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and Cmax of simvastatin, -9 % (90 % CI -23; 8) and -23 % (90 % CI -37; -6) respectively. Clinical PK interactions with CYP3A4 substrates are unlikely.

In a clinical PK study, co-administration of TAGRISSO with fexofenadine (PXR/P-gp substrate) increased the AUC and Cmax of fexofenadine by 56 % (90 % CI 35, 79) and 76 % (90 % CI 49, 108) after a single dose and 27 % (90 % CI 11, 46) and 25 % (90 % CI 6, 48) at steady state, respectively. Patients taking concomitant medications with disposition dependent upon P-gp and with narrow therapeutic index (e.g. digoxin, dabigatran, aliskiren) should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving TAGRISSO (see section 5.2).

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential must avoid becoming pregnant while receiving TAGRISSO. Patients should be instructed to use effective contraception for the following periods after completion of treatment with TAGRISSO: at least 6 weeks for females and 4 months for males.

Pregnancy

TAGRISSO is contraindicated during pregnancy and in women of childbearing potential not using contraception (see section 4.3). Based on its mechanism of action and preclinical data, TAGRISSO may cause foetal harm when administered to a pregnant woman. Administration of TAGRISSO to pregnant rats was associated with embryolethality, reduced foetal growth and neonatal death at exposures similar to what is expected in humans.

Breastfeeding

Breastfeeding is contra-indicated when taking TAGRISSO.

It is not known whether TAGRISSO or its metabolites are excreted in human milk.

Administration to rats during early lactation was associated with adverse effects, including reduced growth rates and neonatal death.

Fertility

Results from animal studies have shown that TAGRISSO has effects on male and female reproductive organs and could impair fertility.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

a. Summary of the safety profile

Studies in EGFR mutation-positive NSCLC patients:

The data described below reflect exposure to TAGRISSO in 1 479 patients with EGFR mutation positive non-small cell lung cancer. These patients received TAGRISSO at a dose of 80 mg daily in three randomised Phase 3 studies (ADAURA, adjuvant; FLAURA, first line and AURA3, second line only), two single-arm studies (AURAex and AURA2, second line or later) and one Phase 1 study (AURA1, first-line or later) (see section 5.1). Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (47 %), rash (45 %), paronychia (33 %), dry skin (32 %) and stomatitis (24 %). Grade 3 and Grade 4 adverse reactions across the studies were 10 % and 0,1 %, respectively. In patients treated with TAGRISSO 80 mg

once daily, dose reductions due to adverse reactions occurred in 3,4 % of the patients. Discontinuation due to adverse reactions was 4,8 %.

Patients with a 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 msec) were excluded from these studies. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

b. Tabulated list of adverse reactions

Adverse reactions have been assigned to the frequency categories in Table 2 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the 1 479 EGFR mutation positive NSCLC patients who received TAGRISSO at a dose of 80 mg daily in the ADAURA, FLAURA, AURA3, AURAex, AURA 2 and AURA1 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

The following side effects have been reported from clinical trials. The following definitions of frequency are used:

Very Common: ≥ 10 %

Common: ≥ 1 % and < 10 %

Uncommon: ≥ 0,1 % and < 1 %

Rare: ≥ 0,01 % and < 0,1 %

Very Rare: < 0,01 %

Table 2. Adverse reactions reported in ADAURA, FLAURA and AURA studies[a]

MedDRA SOC	**MedDRA term**	**CIOMS descriptor/ overall frequency (all CTCAE grades)[b]**	**Frequency of CTCAE grade 3 or higher [b]**
Metabolism and	Decreased appetite	Very common (19 %)	1,1 %

nutrition disorders			
Respiratory, thoracic and mediastinal disorders	Epistaxis	Common (5 %)	0
	Interstitial lung disease[c]	Common (3,7 %)[d]	1,1 %
Gastrointestinal disorders	Diarrhoea	Very common (47 %)	1,4 %
	Stomatitis[e]	Very common (24 %)	0,5 %
Eye disorders	Keratitis[f]	Uncommon (0,7 %)	0,1 %
Skin and subcutaneous tissue disorders	Rash[g]	Very common (45 %)	0,7 %
	Paronychia[h]	Very common (33 %)	0,4 %
	Dry skin[gi]	Very common (32 %)	0,1 %
	Pruritus[j]	Very common (17 %)	0,1 %
	Alopecia	Common (4,6 %)	0
	Urticaria	Common (1,9 %)	0.1 %
	Palmar-plantar erythrodysaesthesia syndrome	Common (1,7 %)	0
	Erythema multiforme[k]	Uncommon (0,3 %)	0
	Cutaneous vasculitis	Uncommon (0,3 %)	0
	Stevens-Johnson syndrome[m]	Rare (0,02 %)	
Investigations	QTc interval prolongation[n]	Uncommon (0,8 %)	
(Findings based on test results presented as CTCAE grade shifts)	Leucocytes decreased[o]	Very common (65 %)	1,2 %
	Lymphocytes decreased[mo]	Very common (62 %)	6,1 %
	Platelet count decreased[mo]	Very common (53 %)	1,2 %
	Neutrophils decreased[o]	Very common (33 %)	3,2 %
	Blood creatinine	Common (9 %)	0

	increased[o]		

[a] Data is pooled from ADAURA, FLAURA and AURA (AURA3, AURAex, AURA 2 and AURA 1) studies; only events for patients receiving at least one dose of TAGRISSO as their randomised treatment are summarised.

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

[c] Includes: interstitial lung disease, pneumonitis.

[d] 5 CTCAE grade 5 events (fatal) were reported.

[e] Includes: mouth ulceration, stomatitis.

[f] Includes: corneal epithelium defect, corneal erosion, keratitis, punctate keratitis.

[g] Includes: acne, dermatitis, dermatitis acneiform, drug eruption, erythema, folliculitis, pustule, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, skin erosion.

[h] Includes: nail bed disorder, nail bed infection, nail bed inflammation, nail discolouration, nail disorder, nail dystrophy, nail infection, nail pigmentation, nail ridging, nail toxicity, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[i] Includes: dry skin, eczema, skin fissures, xeroderma, xerosis.

[j] Includes: eyelid pruritus, pruritus, pruritus generalised.

[k] Five of the 1 479 patients in the ADAURA, AURA and FLAURA studies reported erythema multiforme. Post-marketing reports of erythema multiforme have also been received, including 7 reports from a post-marketing surveillance study (n = 3 578).

[l] Estimated frequency. The upper limit of the 95 % CI for the point estimate is 3/1142 (0,3 %).

[m] One event was reported in a post-marketing study, and the frequency has been derived from the ADAURA, FLAURA and AURA studies and the post-marketing study (n = 5057).

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

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

c. Description of selected adverse reactions

Interstitial lung disease (ILD)

In the ADAURA, FLAURA and AURA studies, the incidence of ILD was 11 % in patients of Japanese ethnicity, 1,6 % in patients of non-Japanese Asian ethnicity and 2,5 % in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 84 days (see section 4.4).

QTc prolongation

Of the 1 479 patients in ADAURA, FLAURA and AURA studies treated with TAGRISSO 80 mg, 0,8 % of patients (n= 12) were found to have a QTc greater than 500 msec, and 3,1 % of patients (n= 46) 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 dysrhythmias were reported in the ADAURA, FLAURA or AURA studies (see sections 4.4 and 5.1).

Gastrointestinal effects

In the ADAURA, FLAURA and AURA studies, diarrhoea was reported in 47 % of patients of which 38 % were Grade 1 events, 7,9 % Grade 2 and 1,4 % were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0,3 % of patients and dose interruption in 2 %. Four events (0,3 %) led to discontinuation. In ADAURA, FLAURA and AURA3 the median time to onset was 22 days, 19 days and 22 days, respectively, and the median duration of the Grade 2 events was 11 days, 19 days and 6 days, respectively.

Haematological events

Early reductions in the median laboratory counts of leukocytes, lymphocytes, neutrophils and platelets have been observed in patients treated with TAGRISSO, which stabilised over time and then remained above the lower limit of normal. Adverse events of leukopenia, lymphopenia, neutropenia and thrombocytopenia have been reported, most of which were mild or moderate in severity and did not lead to dose interruptions.

Elderly

In ADAURA, FLAURA and AURA3 (n= 1 479), 43 % of patients were 65 years of age and older, and 12 % 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) (16 % versus 9 %). The types of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (13 % versus 8 %). 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.

Low body weight

Patients receiving TAGRISSO 80 mg with low body weight (< 50 kg) reported higher frequencies of Grade ≥3 adverse events (46 % versus 31 %) and QTc prolongation (12 % versus 5 %) than patients with higher body weight (≥ 50 kg).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific treatment in the event of TAGRISSO overdose. Medical practitioner should follow general supportive measures and should treat symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01EB04.

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

In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising mutant and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC50s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC50s 480 nM to 1,9 µM against phospho-EGFR). In vivo oral administration of osimertinib lead to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Cardiac electrophysiology

The QTc 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 QTc intervals. A pharmacokinetic /pharmacodynamic analysis with osimertinib predicted a medicine-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90 % CI).

Clinical efficacy and safety

Adjuvant treatment of EGFR mutation positive NSCLC, with or without prior adjuvant chemotherapy – ADAURA

ADAURA was a randomised, double-blind, placebo-controlled study. Eligible patients with resectable tumours stage IB – IIIA (according to American Joint Commission on Cancer [AJCC] 7th edition) were required to have EGFR mutations (Ex19del or L858R). The major efficacy outcome measure was disease free survival (DFS).

Patients with stage II-IIIA disease treated with TAGRISSO compared to placebo, achieved 83% reduction in the risk of disease recurrence or death (median not calculated (NC) and 19.6 months, respectively, HR=0.17, 99.06% CI:0.11, 0.26; P<0.0001). The overall population (IB-IIIA) treated with TAGRISSO compared to placebo demonstrated 80% reduction in the risk of disease recurrence or death (median NC and 27.5 months, respectively, HR=0.20, 99.12% CI: 0.14, 0.30; P<0.0001). Overall survival (OS) data were not mature at the time of DFS analysis.

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterised in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14,3 l/h, apparent volume of distribution is 918 l and terminal half-life of approximately 44 hours. The AUC and Cmax increased dose proportionally over 20 to 240 mg dose range. Administration of osimertinib once daily results in approximately 3-fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady state, circulating plasma concentrations are typically maintained within a 1,6 fold range over the 24-hour dosing interval.

Absorption

Following oral administration of osimertinib, peak plasma concentrations of osimertinib was achieved with a median (min-max) t_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of osimertinib is 70 % (90 % CI 67, 73). Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase 6 % (90 % CI -5; 19) and C_{max} decrease -7 % (90 % CI -19; 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7 % and 2 %, respectively) with the 90 % CI for exposure ratio contained within the 80-125 % limit.

Distribution

Population estimated mean volume of distribution at steady state (V_{SS}/F) of osimertinib is 918 L indicating extensive distribution into tissue. Plasma protein binding could not be measured due to instability but based on the physicochemical properties of osimertinib plasma protein binding is likely to be high. Osimertinib has also been demonstrated to bind covalently to human plasma proteins, human serum albumin and human hepatocytes.

Biotransformation

In vitro studies indicate that osimertinib is metabolised predominantly by CYP3A4, and CYP3A5. Based on in vitro studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of humans 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) tmax of 24 (4-72) and 24 (6-72) hours, respectively. Parent osimertinib accounted for 0,8 %, with the 2 metabolites contributing 0,08 % and 0,07 % of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10 % each of the exposure of osimertinib at steady state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. At least 12 components were observed in the pooled urine and faecal samples in humans with 5 components accounting for >1 % of the dose of which unchanged osimertinib, AZ5104 and AZ7550, accounted for approximately 1,9; 6,6 and 2,7 % of the dose while a cysteinyl adduct (M21), and an unknown metabolite (M25) accounted for 1,5 % and 1,9 % of the dose, respectively.

Based on in vitro studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Based on *in vitro* studies, osimertinib is not an inhibitor of UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Excretion

Following a single oral dose of 20 mg, 67,8 % of the dose was recovered in faeces (1,2 % as parent) while 14,2 % of the administered dose (0,8 % as parent) was found in urine by 84 days of sample collection. Unchanged osimertinib accounted for approximately 2 % of the elimination with 0,8 % in urine and 1,2 % in faeces.

Interactions with transport proteins

In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3. *In vitro*, osimertinib does not inhibit P-g, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 at clinically relevant concentrations.

Based on *in vitro* studies, osimertinib is a substrate of P-g and BCRP but at clinical doses, clinically relevant interactions are unlikely. Based on *in vitro* data, osimertinib is an inhibitor of BCRP (see section 4.5)

Special populations:

In a population based PK analysis (n=1 367), no clinically significant relationships were identified between predicted steady-state exposure (AUCss) and patient's age (range: 25 to 91 years), gender (65 % female), all ethnicity, line of therapy and smoking status (n = 34 current smokers, n = 419 former smokers). Population PK analysis indicated that body weight was a significant covariate with a less than 20 % change in osimertinib AUCss expected across a body weight range of 88 kg to 43 kg respectively (95 % to 5 % quantiles) when compared to the AUCss for the median body weight of 61 kg. Taking the extremes of body weight into consideration, from <43 kg to >89 kg, AZ5104 metabolite ratios ranged from 11,8 % to 9,6 % while for AZ7550 it ranged from 12,8 % to 8,1 %, respectively. Based on population PK analysis, serum albumin was identified as a significant covariate with a -30 % change in osimertinib AUCss expected across the albumin range of 29 to 46 g/l respectively (95 % to 5 % quantiles) when compared to the AUCss for the median baseline albumin of 39 g/l. These

exposure changes due to body weight or baseline albumin differences are not considered clinically relevant.

Hepatic impairment

Osimertinib is eliminated mainly via the liver. In a clinical trial, patients with mild hepatic impairment (Child Pugh A, n=7) or moderate hepatic impairment (Child Pugh B, n = 5) had no increase in exposure compared to patients with normal hepatic function (n=10) after a single 80 mg dose of TAGRISSO. A pharmacokinetic trial in subjects with hepatic impairment has not been conducted. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2,5x upper limit of normal (ULN), or if due to underlying malignancy, >5,0x ULN or with total bilirubin >1,5x ULN. Based on a pharmacokinetic analysis of 134 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin between 1,0 to 1,5x 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 1 216 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), osimertinib exposures were similar. There is no data available on patients with severe hepatic impairment (see section 4.2)

Renal impairment

A pharmacokinetic study in patients with renal impairment has not been conducted. Based on a population PK analysis of 593 patients with mild renal impairment (CLcr 60 to less than 90 ml/min), 254 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 502 patients with normal renal function (greater than or equal to 90 ml/min), osimertinib exposures were similar. Severe renal impairment may influence the elimination of hepatically eliminated medicines. Patients with CLcr less than 15 ml/min were not included in the clinical trials.

5.3 Preclinical safety data

The main findings observed in repeat dose toxicity studies in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including

tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing with the exception of partial recovery for some of the corneal changes.

Osimertinib penetrated the intact blood-brain barrier of the cynomolgus monkey (i.v. dosing), rat and mouse (oral administration).

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

Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays. Osimertinib showed no carcinogenic potential when administered orally to Tg rasH2 transgenic mice for 26 weeks.

Reproductive toxicity

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

Based on studies in animals, female fertility may be impaired by treatment with osimertinib. In repeat dose toxicity studies, an increased incidence of anoestrus, corpora lutea degeneration in the ovaries andepithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for ≥1 month at clinically relevant plasma concentrations. Findings in the ovaries seen following 1month dosing were reversible. In a female fertility study in rats, administration of osimertinib at 20 mg/kg/day (approximately equal to the recommended daily clinical dose of 80mg) 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 off-dose.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol

Microcrystalline cellulose

Low-substituted hydroxypropyl cellulose

Sodium stearyl fumarate

Tablet coating:

Polyvinyl alcohol

Titanium dioxide

Macrogol 3350

Talc

Yellow iron oxide

Red iron oxide

Black iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep out of reach of children.

Store in the original package until required for use.

6.5 Nature and contents of container

Silver aluminium/aluminium blister packs of 10 tablets (3 x 10) packed in a carton.

6.6 Special precautions for disposal

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

AstraZeneca Pharmaceuticals (Pty) Limited

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South Africa

8 REGISTRATION NUMBERS

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TAGRISSO 80 mg: 51/26/0928

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10 DATE OF REVISION OF THE TEXT

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