Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: http://www.gmc-uk.org/mobile/14327

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to licence such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

December 2015
MHRA

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Osimertinib (AZD9291) 40 mg film-coated tablets
Osimertinib (AZD9291) 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 40 mg tablet contains a dose of 40 mg osimertinib (as mesylate).
Each 80 mg tablet contains a dose of 80 mg osimertinib (as mesylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The osimertinib 40 mg tablet is a plain round, biconvex beige film coated tablet.
The osimertinib 80 mg tablet is a plain, oval, biconvex beige film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy.

4.2 Posology and method of administration

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

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

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

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

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

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

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

Table 1. Osimertinib dose adjustment information for adverse reactions

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

	Grade 0-2 after withholding for up to 3 weeks	

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
ECGs: Electrocardiograms; QTc: QT interval corrected for heart rate.

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

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

Renal impairment
No dose adjustment is recommended in patients with mild and moderate renal impairment. Limited data are available in patients with severe renal impairment. The safety and efficacy of osimertinib has not been established in patients with end-stage renal disease [creatinine clearance (CLcr) <15 mL/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end stage renal impairment (see section 5.2).

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

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
St. John's wort should not be used together with osimertinib (see section 4.5).

4.4 Special warnings and precautions for use

Assessment of EGFR T790M mutation status

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

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

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

Interstitial lung disease (ILD)

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

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

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

QTc interval prolongation

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Active substances that may decrease osimertinib plasma concentrations
In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced by 78% when co-administered with rifampicin (600 mg daily for 21 days). Similarly, the exposure to metabolite, AZ5104 decreased by 82% for the AUC and 78% for C_{max}. It is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with osimertinib should be avoided. Moderate CYP3A4 inducers (e g bosentan, efavirenz, etravirine, modafinil) may also decrease osimertinib exposure and should be used with caution, or avoided when possible. There are no clinical data available to recommend a dose adjustment of osimertinib. Concomitant use of St. John's Wort is contraindicated (see section 4.3).

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

Active substances whose plasma concentrations may be altered by osimertinib
Based on *in vitro* studies, osimertinib is a competitive inhibitor of BCRP transporters.

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

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

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving osimertinib. Patients should be advised to use effective contraception for the following periods after completion of treatment with this medicinal product: at least 2 months for females and 4 months for

males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions
Table 2 lists the incidences of adverse reactions commonly reported in patients receiving osimertinib.

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

Table 2. Adverse drug reactions reported in AURA[a] studies

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3-4
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[c]	Common (2.7%)[d]	0.7%
Gastrointestinal disorders	Diarrhoea	Very common (42%)	1%
	Stomatitis	Very common (12%)	0%
Skin and subcutaneous tissue disorders	Rash[e]	Very common (41%)	0.5%
	Dry skin[f]	Very common (31%)	0%
	Paronychia[g]	Very common (25%)	0%
	Pruritus	Very common (14%)	0%
Investigations (findings based on test results presented as CTCAE grade shifts)	Platelet count decreased[h]	Very common (54%)	1.2%
	Leucocytes decreased[h]	Very common (67%)	1.2%
	Neutrophils decreased[h]	Very common (33%)	3.4%

[a] Data is cumulative from AURA extension (Phase II) and AURA 2 studies; only events for patients receiving at least one dose of osimertinib are summarized.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c] Includes cases reported within the clustered terms: Interstitial lung disease and pneumonitis.
[d] 4 CTCAE grade 5 events (fatal) were reported.
[e] Includes cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform.
[f] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema.
[g] Includes cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.
[h] Represents the incidence of laboratory findings, not of reported adverse events.

Description of selected adverse reactions

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

QTc interval prolongation
Of the 411 patients in AURAex and AURA2, one patient (less than 1%) was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis with osimertinib predicted a concentration-dependent increase in

QTc interval prolongation. No arrhythmic events were reported in AURAex or AURA2 (see sections 4.4 and 5.1).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions for patients on EAMS is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with the training provided and the pharmacovigilance protocol

4.9 Overdose

In phase I/II clinical trials a limited number of patients were treated with osimertinib daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with osimertinib 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 osimertinib in error, without any resulting clinical consequences.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Pharmacodynamic effects
In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising-mutant and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC_{50}s 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 IC_{50}s 480 nM to 1.8 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 analysis predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

Clinical efficacy and safety

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

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

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

Table 3. Efficacy results from AURA studies

	Phase I	**Phase II**		
Efficacy Parameter[1]	**AURA (PhI Expansion) (N=63)**	**AURAex (Phase II) (N=201)**	**AURA2 (N=210)**	**Overall (N=411)**
Objective Response Rate[2,3] % (95% CI)	62 (48, 74)	61(54, 68)	71 (64, 77)	66 (61, 71)
Duration of Response (DoR)[3] Median, Months (95% CI)	9.7 (8.3, NE)	NE (NE, NE)	7.8 (7.1, NE)	NE (8.3, NE)

% DoR greater than 6 months (95% CI)	72 (54,84)	83 (74, 89)	75 (65, 82)	78 (72, 84)
Disease Control Rate (DCR)[3] % (95% CI)	95 (86, 99)	90 (85, 94)	91 (87, 95)	91 (88, 94)
Progression-free survival Median, Months (95% CI)	11 (7, 15)	NE (8.1, NE)	8.6 (8.3, 9.7)	9.7 (8.3, NE)

[1] Based on BICR, Blinded Independent Central Review, PFS follow-up.
[2] Objective Response Rate determined by RECIST v1.1 by BICR in the evaluable for response population (measurable disease at baseline by BICR) n=60,199,199,398 for AURA, AURAex, AURA2 and Overall respectively; NE, not estimable, includes 2 complete responses.
[3] Based on patients with response only; DoR defined as the time from the date of first documented response (confirmed complete response or partial response, or stable disease ≥6 weeks).

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

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

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

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

5.2 Pharmacokinetic properties

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

Absorption
Following oral administration of osimertinib, peak plasma concentrations of osimertinib were achieved with a median (min-max) t_{max} of 6 (3 - 24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of osimertinib has not been determined. Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase by 6% (90% CI -5, 19) and C_{max}

decrease by 7% (90% CI -19, 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution

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

Biotransformation

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. CYP3A4 mediated metabolism may be a minor pathway. Alternative metabolic pathways may exist which have not been fully characterized. Based on *in vitro* studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to 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 human plasma, parent osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady-state .

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

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

Elimination

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

Interactions with transport proteins

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

Effects of osimertinib on P-gp and BCRP

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

4.5).

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

Hepatic impairment
Osimertinib is eliminated mainly via the liver, and hence, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in subjects with hepatic impairment has not been conducted. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying malignancy, >5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 44 patients with mild hepatic impairment and 330 patients with normal hepatic function osimertinib exposures were similar. There are limited data available on patients with hepatic impairment (see section 4.2).

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

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

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

Reproductive toxicity

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Mannitol
Microcrystalline cellulose
Low-substituted hydroxpropyl cellulose
Sodium stearyl fumarate

Tablet coating:

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottle with a white polypropylene (PP) child-resistant screw cap. Pack sizes of 25 tablets.

6.6 Special precautions for disposal

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

7. SCIENTIFIC OPINION HOLDER

AstraZeneca UK Ltd
600 Capability Green
Luton
LU1 3LU

8. EAMS NUMBER(S)

17901/0001

9. DATE OF EAMS SCIENTIFIC OPINION/RENEWAL OF THE SCIENTIFIC OPINION

4th December 2015

Additional information:

• Each prescribing physician will be provided with a **physician pac**k containing all the relevant documents needed to manage patients receiving osimertinib under EAMS.

• As each patient gives **informed consent**, they must be issued with a **Patient Alert Card**. This is credit-card sized and patients must be instructed to carry it with them at all times. It summarises the symptoms of Interstitial Lung Disease and gives advice on what to do if they develop. The alert card also advises patients to contact their doctor immediately if they become pregnant (or father a child) or take too many tablets. In addition it alerts any other healthcare professional that may treat them, that the patient is receiving osimertinib through an early access scheme and provides details of their physician and their contact details

• Prescribers will be provided with training and guidance documents on the safety reporting requirements and processes. All adverse events experienced by patients in the osimertinib EAMS should be reported to AstraZeneca from the start of treatment. The training must be completed before a patient commences the EAMS.

• On completion of the training prescribers will need to submit a **Patient Access Form** to register individual patients and sign a **Declaration** to ensure eligibility within the scheme. • Following approval by AstraZeneca, physician must submit an **EAMS Re-Supply** Form every 3 months to receive continuing supplies of osimertinib.
Contact information: Email: astrazenecaUKMCdrugsafety@astrazeneca.com Telephone number for AstraZeneca UK Limited: 0800 783 0033