Summary of the Risk Management Plan (RMP) for

Tagrisso® (Osimertinib)

40 mg and 80 mg, filmcoated tablets

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Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Tagrisso is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Tagrisso in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. AstraZeneca AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Tagrisso.

This is a summary of the Risk Management Plan (RMP) for TAGRISSO® (osimertinib). The RMP details important risks of TAGRISSO, how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) of TAGRISSO®.

The TAGRISSO™ summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how TAGRISSO® should be used.

This summary of the RMP for TAGRISSO® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of the TAGRISSO® RMP

1 The medicine and what it is used for

TAGRISSO™ is authorised 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, the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations or the adjuvant treatment after complete tumour resection in adult patients with NSCLC whose tumours have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations. It contains osimertinib as the active substance and it is given as a 40mg or 80mg tablet for once daily oral administration.

TAGRISSO™ is authorised in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of TAGRISSO®, together with measures to minimise such risks and the proposed studies for learning more about the risks of TAGRISSO®, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

2.1 List of important risks and missing information

Important risks of TAGRISSO® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks

can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TAGRISSO®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 1 List of important risks and missing information

Important identified risks	・Interstitial lung disease ・Cardiac failure
Important potential risks	・None
Missing information	・None

2.2 Summary of important risks

This section presents a summary of important identified risks, important potential risks and missing information.

Table 1 Important identified risks – Interstitial Lung Disease

Evidence for linking the risk to the medicine	The development of ILD-like events was prospectively identified as a potential safety concern from a review of the use of other EGFR TKI medications and was therefore considered a topic of special interest in the osimertinib clinical development programme. Following evaluation of all available data, ILD was added as a listed ADR in section "*Undesirable effects"* of the osimertinib SmPC, and wording relating to the detection and management of potential/confirmed events of ILD was implemented in section *"Special warnings and precautions for use"* and section *"Posology and method of administration".* The ADAURA placebo-controlled trial (DCO 11 April 2022) provides conclusive evidence of the osimertinib-related nature of ILD observed in these patients. No patients in the placebo arm were diagnosed with ILD, as opposed to 11 patients in the osimertinib arm who were diagnosed with ILD. All reported events were considered to be either mild or moderate in severity (6 patients [1.8%] with maximum CTCAE Grade 1 events, and 5 patients [1.5%] with maximum CTCAE Grade 2 events), and all patients were reported to have recovered. Only 2 event were reported as SAEs (due to hospitalisation). The recent FLAURA2 study investigating the addition of chemotherapy to an osimertinib regimen did not increase the incidence or severity of ILD events when compared with osimertinib monotherapy (3.3% Osimertinib plus chemotherapy vs 3.6% osimertinib monotherapy).
Risk factors and risk groups	ILD has been noted as a potentially life-threatening complication of treatment with other EGFR TKI medications (erlotinib, gefitinib and afatinib), and is typically observed within the first month of therapy. Risk factors include previous chemotherapy treatment, previous radiation therapy to the lungs, pre-existing parenchymal lung disease, metastatic

Table 1 Important identified risks – Interstitial Lung Disease

	lung disease, concomitant pulmonary infection (Cataldo et al 2011) and previous or concurrent IO (immune-oncology) therapy (Adderley et al 2021). Kudoh and colleagues report that other risk factors of ILD include older age, poor ECOG performance status (≥2), smoking, recent NSCLC diagnosis, reduced normal lung on CT scan, pre-existing chronic ILD, concurrent cardiac disease, and Japanese ethnicity (Kudoh et al 2008). In a case control study of 227 ILD patients from the Lung Tissue Research Consortium based in the US, an EGFR mutation associated with EGFR level changes and increased cancer risk, also demonstrated an elevated risk of ILD (OR=1.33, 95% CI=1.07–1.66, P=0.0099) with the A allele frequency being significantly higher in the cases (64%) than the controls (57%). The genotype association remained significant after adjusting for age and gender (P=0.0087) (Li et al 2014a).
Risk minimisation measures	*Routine risk minimisation measures:* • SmPC section "*Undesirable effects*". • SmPC section "*Posology and method of administration"* and section "*Special warnings and special precautions for use"*.
PV activitiy	*Routine PV activity:* Follow-up targeted safety questionnaire

Table 2 Important identified risks – Cardiac failure

Evidence for linking the risk to the medicine	In the in vitro pharmacology studies, osimertinib and metabolites AZ5104 and AZ7550 were shown to inhibit HER2 (also known as erbB2) in the context of cancer cell lines. HER2 inhibition has previously been associated with a potential risk of a decrease in LVEF in some patients given trastuzumab following anthracycline-based therapy (Ewer and O'Shaughnessy 2007); however, analyses of LVEF in more recent HER2 small molecule inhibitors, including irreversible inhibitors, shows the link between HER2 inhibition and LVEF decrease is not conclusive (Ades et al 2014, Ewer et al 2014, Perez et al 2008). Additionally, more recent HER2 inhibitors (e.g. afatinib) have been shown not to be associated with this risk (Ewer et al 2015). Whilst there is no direct evidence that inhibition of erbB2 is linked with cardiac failure or LVEF decreases, the understanding of the role of erbB2 inhibitors in cardiac function is not fully elucidated, and there is therefore a potential risk of a role for erbB2 in the stress/recovery response to cardiac damage (e.g. myocardial infarction). In consideration of this mechanistic hypothesis, AstraZeneca, in consultation with internal and external experts, put in place a clinical cardiac monitoring plan in order to evaluate the potential impact of

Table 2 Important identified risks – Cardiac failure

	osimertinib on LVEF. Routine monitoring of AEs, including external cardiologist review, assess a potential drug involvement in the aetiology and recovery of cardiac events. Upon review of the data obtained in the AURA3 study, a numerical imbalance in the number of patients with an AE from the Cardiac failure or Cardiomyopathy SMQs, and in LVEF decreases between the 2 treatment arms (TAGRISSO® versus chemotherapy) was noted. A similar numerical imbalance was also noted between treatment arms (TAGRISSO® versus standard of care therapy [erlotinib or gefitinib]) in the FLAURA study. However, in a placebo controlled trial (ADAURA), there was no difference between treatment arms in the number of patients who experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50% in either patients treated with TAGRISSO® or patients treated with placebo, 1.5% (5/337); 1.5% (5/343), respectively. A numerical imbalance was observed in the incidence of cardiac effects events (cardiomyopathy or cardiac failure SMQs) in osimertinib plus chemotherapy (9.4%) when compared to osimertinib monotherapy (3.6%) in the FLAURA2 study. This difference was primarily driven by adverse events of ejection fraction decreased. Overall, a review of AEs indicative of cardiac failure was comparable with the type and frequency of AEs reported in the osimertinib monotherapy clinical development programme to date; no new safety signal for cardiac effects was identified. On a study population level, no notable changes in cardiac contractility (as measured by LVEF) over time were observed in either treatment arm. In the osimertinib + chemotherapy arm, median LVEF at baseline was 65.0%, which remained stable over time, with a lowest recorded median LVEF value of 64.0%. In the osimertinib arm, median LVEF was 66.0% at baseline, which remained stable over time, with a lowest recorded median LVEF value of 64.0% . Events of cardiac failure were observed in patients with underlying risk factors which could put patients at higher risk. The benefit risk profile of osimertinib and chemotherapy has not been impacted such that additional risk minimisation measures or further characterisation are warranted.
Risk factors and risk groups	Risk factors for the development of cardiac failure (NHLBI, 2017) include: • Age (increased risk in patients over 65 years) and race (increased risk in Black patients compared to those from other races) • Other cardiac conditions such as arrhythmia, cardiomyopathy, congenital heart defects, or cardiac valve disease • Coronary heart disease • Previous cardiac damage from myocardial infarction • Diabetes or other metabolic diseases • Severe obesity • Long-term alcoholism or drug abuse • Long-term high blood pressure

Table 2 Important identified risks – Cardiac failure

	• Prior cancer treatments, e.g. anthracyclines or radiotherapy to the chest In order to facilitate the assessment of potential risks factors for change in LVEF measurements (as a precursor to the undesirable clinical outcome of cardiac failure) in osimertinib-treated patients, an exposure-response analysis, designed to explore a potential relationship between osimertinib PK exposure and decrease in minimum or maximum change from baseline LVEF measurement and LVEF events using data from the AURA, AURA2, AURA3 and FLAURA studies was performed. The analysis did not identify any covariates potentially confounding the exposure-to-LVEF event probability relationship, although there was an indication that patients of White ethnicity have a higher LVEF event risk than Asians or other ethnicities. Several covariates of medical history, i.e., hypertension, statin use, diabetes, ischemic heart disease, heart failure, coronary artery disease, hypothyroidism, and hypoalbuminemia were also tested. An indication for relationship with LVEF event probability was not identified for any of these covariates. Medical history of myocardial infarction, cardiomyopathy, and aortic stenosis were not considered as there were only very small numbers of occurrences.
Risk minimisation measures	*Routine risk minimisation measures:* • SmPC section "Undesirable effects" "cardiac failure and LVEF decreased only". • SmPC section "*Special warnings and special precautions for use"*.
PV activitiy	*Routine PV activity:* Follow-up targeted safety questionnaire

Table 3 Missing information

There are currently no outstanding items of missing information for TAGRISSO.

2.3 Post authorisation development plan

2.3.1 Studies which are conditions of the marketing authorization

Not applicable.

2.3.2 Other studies in post-authorisation development plan

There are no studies which are a condition of the marketing authorisation for TAGRISSO.