ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Aumseqa 55 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains aumolertinib mesilate equivalent to 55 mg aumolertinib.

Excipients with known effect

Each film-coated tablet contains 15.3 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light yellow, 7 mm, round immediate release tablet debossed with “E1” on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aumseqa as monotherapy is indicated for:
- the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (for biomarker-based patient selection, see section 4.2).
- the treatment of adult patients with advanced EGFR T790M mutation-positive NSCLC (for biomarker-based patient selection, see section 4.2).

4.2 Posology and method of administration

Treatment with Aumseqa should be initiated by a physician experienced in the use of anticancer medicinal products.

Patient selection

EGFR mutation status in tumour or plasma specimens should be assessed by a CE-marked IVD with the corresponding intended purpose. If the CE-marked IVD is not available, an alternative validated test should be used (see section 4.4).

Posology

The recommended dose of Aumseqa is 110 mg (2 tablets of 55 mg) once a day.

This medicinal product should be continued until disease progression or unacceptable toxicity.

Missed dose
If a dose of Aumseqa is missed, it should be taken within the same day as soon as the patient remembers. However, if the next scheduled dose is due within 12 hours, then the missed dose must be skipped. The patient should not take two doses together to make up for a missed dose.

QTc interval prolongation
An electrocardiogram (ECG) must be performed prior to treatment initiation, at least once during the first 3 weeks of therapy, and periodically thereafter as clinically indicated. QTc interval abnormalities should be managed promptly (see Table 1 and section 4.4).

Cardiac failure
For patients with known cardiovascular risk factors and conditions which may affect left ventricular ejection fraction (LVEF), cardiac function should be monitored, with at least LVEF assessment prior to treatment initiation and during treatment with Aumseqa (see section 4.4).

Co-administration with strong CYP3A4 inhibitors
If concurrent use of strong CYP3A4 inhibitors (such as grapefruit juice, clarithromycin, itraconazole or lopinavir) cannot be avoided, the dose of Aumseqa should be reduced from 110 mg to 55 mg (see section 4.5).

Dose modifications for adverse reactions
Dosing interruption and/or dose reduction or permanent discontinuation may be required based on individual safety and tolerability.

If dose reduction is necessary, then the dose should be reduced from 110 mg (2 tablets) to 55 mg (1 tablet) taken once daily.

Dose modification guidelines for adverse reactions are provided in Table 1.

Table 1. Recommended Aumseqa dose modifications due to adverse reactions

Adverse reaction	Severity	Dose modification
Interstitial lung disease	Any grade	Permanently discontinue Aumseqa.
QTc interval prolongation	QTc interval prolongation > 480 to ≤ 500 msec (Grade 2)	Withhold Aumseqa for up to 2 weeks. If QTc interval has not recovered to ≤ 480 msec, permanently discontinue Aumseqa. If QTc interval recovers to ≤ 480 msec or within 30 msec of baseline, resume treatment at 110 mg. Monitor ECGs at least weekly for 2 weeks following return to ≤ 480 msec. Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see section 4.5).
	QTc interval prolongation > 500 msec or > 60 msec from baseline (Grade 3)	Withhold Aumseqa for up to 2 weeks. If QTc interval has not recovered to ≤ 480 msec or within 30 msec of baseline, permanently discontinue Aumseqa.

		If QTc interval recovers to ≤ 480 msec: • resume treatment at 110 mg dose for the first occurrence. • resume treatment at 55 mg dose for the second occurrence or the first occurrence in patients with risk factors (see section 4.4). Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg). Monitor ECGs at least weekly for 2 weeks following return of QTc interval to ≤ 480 msec. Monitor and supplement electrolyte levels as clinically indicated. Review and adjust concomitant medicinal products with known QTc interval prolonging effects (see section 4.5).
	Prolongation associated with torsade de pointes, polymorphic ventricular tachycardia, or signs/symptoms of other serious arrhythmias	Permanently discontinue Aumseqa.
Cardiac failure	Asymptomatic, absolute decrease in LVEF > 10% from baseline or to below 50%	Withhold Aumseqa for up to 2 weeks. If LVEF returns to baseline or ≥ 50%: • resume treatment at 110 mg dose for the first occurrence. • resume treatment at 55 mg dose for the second occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg).
	Symptomatic congestive heart failure	Permanently discontinue Aumseqa.
Blood creatine phosphokinase (CPK) increased / rhabdomyolysis	Grade 3 with muscular symptoms (e.g. muscle tenderness, muscle twitches or myalgia)	Withhold Aumseqa for up to 2 weeks. If muscular symptoms resolve and blood CPK increase is ≤ Grade 3: • resume treatment at 110 mg dose for the first occurrence. • resume treatment at 55 mg for the second occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg). If muscular symptoms do not resolve and CPK increase does not improve to ≤ Grade 2, permanently discontinue Aumseqa.

	Grade 4 with or without muscular symptoms (e.g. muscle tenderness, muscle twitches or myalgia)	Withhold Aumseqa for up to 2 weeks. If muscular symptoms resolve and blood CPK increase is ≤ Grade 3, resume treatment at 55 mg dose for the first occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on this dose. If muscular symptoms do not resolve and CPK increase remains ≥ Grade 3, permanently discontinue Aumseqa.
Other adverse reactions	≥ Grade 3	Withhold Aumseqa for up to 2 weeks. If adverse reaction recovers to ≤ Grade 2: • resume treatment at 110 mg dose for the first occurrence • resume treatment at 55 mg dose for the second occurrence. Permanently discontinue Aumseqa if symptoms/signs recur at any time on the reduced dose (55 mg). If adverse reaction does not recover to ≤ Grade 2, permanently discontinue Aumseqa.

Grade = Severity graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
CPK = creatine phosphokinase, ECG = electrocardiogram, LVEF = left ventricular ejection fraction, QTc = corrected QT

Special populations

No dose modification is required due to patient age, body weight, gender, ethnicity, or smoking status (see section 5.2).

Elderly
No dose modification is required for the elderly (see section 5.2).

Hepatic impairment
Based on clinical studies, no dose modification is required in patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (see section 5.2).

Renal impairment
Based on clinical studies and population pharmacokinetic (PK) analysis, no dose modification is required in patients with mild or moderate renal impairment. Aumolertinib has not been evaluated in patients with severe renal impairment (creatinine clearance [CLc] < 30 mL/min) or end-stage renal disease. Caution should be exercised when using Aumseqa in patients with severe or end-stage renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of Aumseqa in children or adolescents under the age of 18 years have not been established. No data are available.

Method of administration

This medicinal product is for oral use.

Two 55 mg tablets should be swallowed whole with water without chewing or crushing.

Aumseqa should be taken approximately at the same time each day. It can be taken with or without food (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Congenital long QT syndrome (see section 4.4).

Familial history of sudden cardiac death or polymorphic ventricular arrhythmia (see section 4.4).

QT/QTc interval > 500 msec, regardless of the correction method (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

Assessment of EGFR mutation status

When considering the use of Aumseqa as a treatment for patients with locally advanced or metastatic NSCLC, it is necessary to determine the mutation status of EGFR. A validated EGFR mutation test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Positive determination of EGFR mutation status using either a tissue-based or plasma-based test indicates eligibility for treatment with Aumseqa. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tumour tissue-based test wherever possible, as a plasma-based test may provide a false negative result. Only tests with demonstrated utility for the determination of EGFR mutation status should be used.

QTc interval prolongation

QTc interval prolongation has occurred in subjects treated with Aumseqa (see section 4.8). One sudden cardiac death was reported in clinical studies with Aumseqa. Subjects with clinically important cardiac abnormalities in rhythm and conduction, as measured by resting ECG, were excluded from the clinical studies.

Patients should be informed of the risk of QT prolongation, its signs and symptoms (palpitations, dizziness, syncope or even cardiac arrest) and be advised to contact their physician immediately if these occur.

An ECG must be performed prior to treatment initiation, at least once during the first 3 weeks of therapy, and periodically thereafter as clinically indicated. Heart rate corrected QT (QTc) should be less than 480 msec prior to treatment initiation and, in the presence of an abnormal QT, practitioners should thoroughly reassess the benefit/risk of initiating Aumseqa (see section 4.3). In case QTc interval prolongation is between 480 msec and 500 msec, initiation of treatment with Aumseqa should remain exceptional and be accompanied by close monitoring.

Treatment discontinuation and dose modification are recommended in patients who develop confirmed QTc interval prolongation > 480 msec (see section 4.2). Patients with prolonged QTc intervals, who develop symptoms or signs of severe arrhythmia, including, but not limited to, torsade de pointes and ventricular tachycardia, should permanently discontinue treatment with Aumseqa and be immediately treated as per standard of care.

Concomitant administration of medicinal products known to prolong the QTc interval may increase the risk of QTc interval prolongation and should be avoided whenever possible during treatment with

Aumseqa. Patients should be treated with caution and closely monitored for QTc interval prolongation if use of a suitable alternative is not possible (see sections 4.2, 4.5 and 4.8).

Patients with congestive heart failure, electrolyte abnormalities or who are using medicinal products known to prolong the QT interval (see section 4.5) should undergo regular electrocardiogram (ECG) and electrolyte monitoring. In case of severe vomiting and /or diarrhoea, an assessment of serum electrolytes abnormalities, especially hypokalaemia/hypomagnesemia, must be performed (see section 4.2).

Cardiac failure

Cardiac failure, including life threatening or fatal events, have occurred uncommonly in subjects treated with Aumseqa (see section 4.8). Subjects were required to have LVEF > 40% to be included in the clinical studies.

For patients with known cardiovascular risk factors or conditions that may affect LVEF, cardiac function should be monitored, with at least LVEF assessment prior to treatment initiation and during treatment with Aumseqa, as clinically indicated. For patients who develop symptomatic congestive heart failure during treatment, cardiac monitoring including LVEF assessment should be considered, and Aumseqa should be permanently discontinued (see sections 4.2 and 4.8).

Interstitial lung disease (ILD)

ILD has been reported in subjects treated with Aumseqa (see section 4.8). ILD may be fatal or life-threatening. Subjects 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 the clinical studies. Patients with acute episodes and/or exacerbations of pulmonary symptoms (e.g., dyspnoea, cough, or fever) with no clear cause should be investigated for possible ILD during treatment with Aumseqa. Treatment should be interrupted while conducting investigation of these symptoms. If ILD is confirmed, Aumseqa should be permanently discontinued, and appropriate treatment for ILD initiated.

Venous thromboembolic events

Thromboembolic events, including deep vein thrombosis, pulmonary embolism and cerebral infarction, have been reported in subjects treated with Aumseqa, including in subjects receiving anti-thrombotic agents (see section 4.8). If clinical signs and symptoms of thromboembolic events occur or are suspected, patients should be evaluated promptly, followed by appropriate treatment. Aumseqa should be withheld, and the patient stabilised before resuming therapy.

Increased blood creatine phosphokinase (CPK) and risk of rhabdomyolysis

Increased blood CPK occurred in clinical studies at the recommended dose (see section 4.8). While in most cases increased blood CPK was asymptomatic and did not lead to discontinuations, Grade 3 CPK elevations with muscular symptoms and Grade 4 CPK elevations with or without muscular symptoms, indicative of rhabdomyolysis, also occurred.

Blood CPK should be obtained before initiating Aumseqa and periodically during treatment, as clinically indicated.

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination.

Concomitant administration of Aumseqa should be avoided with medicinal products that can increase blood CPK or strong CYP3A4 inhibitors as they may increase the risk of blood CPK elevation and/or muscle symptoms (see section 4.5).

If rhabdomyolysis occurs, Aumseqa should be withheld and treatment for rhabdomyolysis should be initiated as clinically indicated (see section 4.2).

Co-administration with CYP3A4 inhibitors

Co-administration of Aumseqa with moderate or strong CYP3A4 inhibitors should be avoided. If concurrent use of strong CYP3A4 inhibitors (such as grapefruit juice, clarithromycin, itraconazole or lopinavir) cannot be avoided, the dose of Aumseqa should be reduced from 110 mg to 55 mg. (see section 4.5).

Routine monitoring

Renal function
Increased blood CPK (see above) can be associated with acute renal impairment. Renal function should be monitored prior to initiating Aumseqa, and periodically during treatment as clinically indicated.

Liver function
Liver function test abnormalities (including increases in alanine aminotransferase [ALT] aspartate aminotransferase [AST], and blood bilirubin levels) have been observed during treatment with aumolertinib, including rarely reported drug-induced liver injury (DILI). Liver function should be monitored prior to initiating Aumseqa, and periodically during treatment as clinically indicated. The frequency of monitoring may be adjusted according to the severity of liver function abnormalities or symptoms.

Lactose

Aumseqa contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains < 1 mmol sodium (23 mg) per daily dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Active substances that may increase aumolertinib plasma concentrations

Co-administration with CYP3A4 inhibitors
Aumolertinib is mainly metabolised by CYP3A4 enzymes. In a drug-drug interaction (DDI) study, co-administration of aumolertinib with a strong CYP3A4 inhibitor (itraconazole) significantly increased aumolertinib exposure (area under the plasma concentration-time curve [AUC] increased 3.7-fold). Co-administration of Aumseqa with moderate (e.g., verapamil, fluconazole) or strong (e.g., grapefruit juice, clarithromycin, itraconazole, lopinavir) CYP3A4 inhibitors should be avoided. If concurrent use of strong CYP3A4 inhibitors cannot be avoided, the dose of Aumseqa should be reduced from 110 mg to 55 mg (see section 4.2).

Co-administration with BCRP and P-gp inhibitors
Based on *in vitro* data, aumolertinib is a substrate of P-glycoprotein (P-gp) and breast-cancer resistance protein (BCRP). Concomitant administration of aumolertinib with medicinal products that are inhibitors of these transporter proteins should be avoided, as it may result in increased aumolertinib plasma concentrations. If co-administration with such inhibitors is unavoidable, clinical monitoring is recommended.

Active substances that may decrease aumolertinib plasma concentrations

Co-administration with CYP3A4 inducers
In a DDI study, co-administration of aumolertinib with a strong CYP3A4 inducer (rifampicin) decreased aumolertinib exposure (AUC decreased by approximately 90%). Co-administration of Aumseqa with moderate (e.g., bosentan, efavirenz) or strong (e.g., rifampicin, carbamazepine, phenytoin sodium, St. John's wort) CYP3A4 inducers is not recommended.

Potential for aumolertinib to affect the exposure to other medicinal products

CYP3A substrates
Aumolertinib decreased the exposure of midazolam (a sensitive CYP3A substrate) by approximately 27% in a clinical study. Aumolertinib is therefore considered a weak inducer of CYP3A and may decrease concentrations of medicinal products that are CYP3A substrates. Concomitant use with sensitive CYP3A substrates for which small changes in exposure may lead to loss of efficacy (e.g., some hormonal contraceptives, certain oncology or anti-infective agents) or with CYP3A substrates with a narrow therapeutic index (e.g., tacrolimus, cyclosporine, sirolimus, fentanyl) should be avoided. If concomitant use cannot be avoided, clinical response should be monitored and dose adjustment of the CYP3A substrate considered, in accordance with its prescribing information.

Interactions with drug transporters
Based on *in vitro* studies, aumolertinib is an inhibitor of P-glycoprotein (P-gp). In a clinical DDI study, aumolertinib increased the average steady-state maximum concentration (C_{max})and AUC of fexofenadine (sensitive P-gp substrate) by 86% and 67%, respectively. Caution should be taken when administering Aumseqa with medicinal products that are sensitive P-gp substrates with a narrow therapeutic window (e.g., digoxin, dabigatran, colchicine), and these patients should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medicinal products whilst receiving Aumseqa.

Based on an *in vitro* study, aumolertinib is an inhibitor of multidrug and toxin extrusion (MATE)1 and organic cation transporter (OCT)1. No clinical studies have been performed to investigate interactions with MATE1 and OCT1 substrates; therefore, the potential *in vivo* effect of concomitant inhibition of MATE1 or OCT1 by Aumseqa is unknown. Caution is recommended when aumolertinib is co-administered with sensitive MATE1 or OCT1 substrates with a narrow therapeutic index.

Based on an *in vitro* study, aumolertinib is an inhibitor of BCRP. No clinical studies have been performed to investigate interactions with BCRP. Therefore, co-administration of aumolertinib with sensitive BCRP substrates should be avoided. If such co-administration is unavoidable, close clinical monitoring for increased exposure or adverse effects of the BCRP substrate is recommended.

Effect of gastric acid reducing active substances on aumolertinib

No clinically relevant changes in aumolertinib exposure are anticipated with gastric acid reducing agents such as famotidine or omeprazole. Aumseqa may be co-administered with gastric acid reducing agents without dose adjustment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Aumseqa. Female patients should use highly effective contraception during treatment and for 4 weeks after completion of treatment with Aumseqa.
Aumseqa may decrease the efficacy of hormonal contraceptives (see section 4.5). Advise patients to avoid concomitant use with combined hormonal contraceptives (e.g., pill, patch, ring). Females using hormonal contraceptives should be counselled to use an alternative contraceptive method (e.g., non-

hormonal intrauterine system) or additional non-hormonal contraceptive (e.g., condoms) during concomitant use and for 4 weeks after discontinuation of Aumseqa.

Pregnancy

There are no data from the use of aumolertinib in pregnant women. Studies in animals have shown reproductive and developmental toxicity (see section 5.3). Mechanistically, all EGFR targeting medicinal products have the potential to cause foetal harm. Based on its mechanism of action and preclinical data, Aumseqa should not be used during pregnancy.

Breast-feeding

It is unknown whether aumolertinib or metabolites are excreted in human milk. A risk to the breast-feeding newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Aumseqa and for 4 weeks after completion of treatment with Aumseqa.

Fertility

In animal studies, impacts on fertility effects were observed in females (see section 5.3). There are no clinical data on the effect of aumolertinib on human fertility.

4.7 Effects on ability to drive and use machines

Aumseqa has minor influence on the ability to drive and use machines. Fatigue and dizziness have been reported in some patients following administration with Aumseqa. Patients experiencing these symptoms should be advised not to drive or use machines until these symptoms resolve.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions in subjects treated with Aumseqa were aspartate aminotransferase (AST) increased (40.4%), hyponatraemia (37.2%), alanine aminotransferase (ALT) increased (33%), blood CPK increased (31.7%), white blood cell (WBC) count decreased (30.6%), platelet count decreased (29.4%), upper respiratory tract infections (23.3%), and rash (22.8%). The most frequently reported Grade ≥ 3 adverse reaction was blood CPK increased (7.5%).

The most common serious adverse reactions were venous thromboembolism (4.2%), lower respiratory tract and lung infections (2.8%), and urinary tract infection (1.1%).

Treatment discontinuation due to adverse reactions occurred in 2.2% of subjects. The most common adverse reaction leading to treatment discontinuation was ILD, occurring in 0.4% of subjects.

Treatment interruption and dose reduction due to adverse reactions occurred in 12.1% and 3.1% of subjects, respectively. The most common adverse reaction leading to interruption or dose reduction was blood CPK increased (occurring in 6.1% and 2.0% of subjects, respectively); dose interruption due to ALT increased occurred in 1.8% of subjects.

Tabulated list of adverse reactions

The data described in this section reflect exposure to Aumseqa in subjects with EGFR mutation-positive NSCLC. 545 subjects received Aumseqa at the recommended dose of 110 mg once a day in 2 multicentre pivotal studies: 1 phase 3 study in the first-line setting (HS-10296-03-01, AENEAS) and 1 phase 1/2 study in pre-treated subjects (HS-10296-12-01, APOLLO) (see section 5.1).
Adverse reactions reported are presented in Table 2 and listed by system organ class, MedDRA term and frequency with the most frequent reactions listed first.

The following definitions apply to the frequency terminology used hereafter: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000 < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000); not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2. Adverse reactions reported in subjects treated with Aumseqa

System organ class	MedDRA preferred term	Adverse reactions	
		Frequency of all grades	**Frequency of grade ≥ 3**
Infections and infestations	Upper respiratory tract infections [a]	Very common	Uncommon
	Urinary tract infections [b]	Very common	Uncommon
	Lower respiratory tract and lung infection [c]	Common	Common
	Conjunctivitis [d]	Common	-
Blood and lymphatic system disorders	Anaemia	Very common	Common
Immune system disorders	Hypersensitivity	Common	-
Metabolism and nutrition disorders	Hyponatraemia *[e]	Very common	Common
	Hypokalaemia *[f]	Very common	Common
	Decreased appetite	Common	Uncommon
	Hyperuricaemia	Common	-
Eye disorders	Dry eye [g]	Common	-
	Blurred vision [h]	Common	-
	Ocular discomfort [i]	Uncommon	-
	Ocular hyperaemia [j]	Uncommon	-
	Abnormal sensation in eye [k]	Uncommon	-
	Corneal changes [l]	Uncommon	-
	Eyelid oedema [m]	Uncommon	-
Cardiac disorders	Cardiac failure [n]	Uncommon	Uncommon
Vascular disorders	Hypertension [o]	Common	Common
	Venous thromboembolism [p]	Common	Common
Respiratory, thoracic and mediastinal disorders	Cough [q]	Very common	-
	Interstitial lung disease [r]	Common	Uncommon
Gastrointestinal disorders	Diarrhoea	Very common	Uncommon
	Mouth ulceration [s]	Very common	-
	Vomiting	Very common	Uncommon
	Nausea	Common	Uncommon
	Rash [t]	Very common	Uncommon

System organ class	MedDRA preferred term	Adverse reactions	
		Frequency of all grades	Frequency of grade ≥ 3
Skin and subcutaneous tissue disorders	Pruritus	Very common	-
	Paronychia	Common	-
	Dry skin	Common	-
	Dermatitis [u]	Common	-
	Erythema [v]	Uncommon	-
	Palmar-planar erythrodysaesthesia syndrome	Uncommon	-
	Folliculitis	Uncommon	-
Musculoskeletal and connective tissue disorders	Blood creatine phosphokinase increased	Very common	Common
	Rhabdomyolysis	Common	Common
	Pain in extremity	Common	Uncommon
	Myalgia	Common	-
	Muscular weakness	Common	Uncommon
Renal and urinary disorders	Blood creatinine increased *	Very common	Uncommon
	Proteinuria	Common	Uncommon
Investigations	Aspartate aminotransferase (AST) increased *	Very common	Common
	White blood cell (WBC) count decreased *[w]	Very common	Common
	Alanine aminotransferase (ALT) increased *	Very common	Common
	Platelet count decreased *[x]	Very common	Common
	Blood bilirubin increased *[y]	Very common	Uncommon
	Electrocardiogram QT prolonged	Common	Uncommon
	Blood lactate dehydrogenase increased	Common	-
	Gamma-glutamyltransferase increased	Common	Uncommon
	Lymphocyte count decreased	Common	Common

Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
The severity of adverse reactions was assessed based on the CTCAE, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening, and Grade 5 = death.

[a] Includes: acute sinusitis, laryngopharyngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, and upper respiratory tract infection.
[b] Includes: cystitis, pyelonephritis acute, urethritis, and urinary tract infection.
[c] Includes: atypical pneumonia, bronchitis, pneumonia, and sputum purulent.
[d] Includes: conjunctivitis and conjunctivitis allergic.
[e] Includes: blood sodium decreased, hyponatraemia*.
[f] Includes: blood potassium decreased, hypokalaemia*.
[g] Includes: dry eye and xerophthalmia.
[h] Includes: visual impairment and blurred vision.

[i] Includes: eye pain, and ocular discomfort.
[j] Includes: ocular hyperaemia, conjunctival haemorrhage, and eye haemorrhage.
[k] Includes: abnormal sensation in eye, and foreign body sensation in eyes.
[l] Includes: corneal exfoliation and corneal opacity.
[m] Includes: eyelid oedema and swelling of eyelid.
[n] Includes: cardiac failure, cardiac failure chronic, ejection fraction decreased, and pulmonary oedema.
[o] Includes: blood pressure increased, hypertension.
[p] Includes: deep vein thrombosis, pulmonary embolism, venous thrombosis limb, cerebral infarction and cerebral thrombosis.
[q] Includes: cough, productive cough, and upper-airway cough syndrome.
[r] Includes: bronchiolitis, interstitial lung disease, and pneumonitis.
[s] Includes: aphthous ulcer, dry mouth, glossodynia, mouth ulceration, oral pain, stomatitis, and tongue ulceration.
[t] Includes: drug eruption, papule, macule, rash, rash maculo-papular, rash papular, rash pruritic, rash pustular, and urticaria.
[u] Includes: dermatitis and dermatitis acneiform.
[v] Includes: erythema and erythema nodosum.
[w] Includes: neutropenia, neutrophil count decreased, and white blood cell count decreased*.
[x] Includes: platelet count decreased*, and thrombocytopenia.
[y] Includes: blood bilirubin increased, and hyperbilirubinemia.
* Represent incidence of laboratory findings, not of adverse events

Description of selected adverse reactions

Interstitial lung disease (ILD)
In clinical studies (N = 545), ILD was reported in 16 subjects (2.9%) treated with Aumseqa 110 mg. One fatal case of ILD was reported. The median time-to-onset of ILD was 124 days (range: 2 days – 932 days). The median time-to-resolution of ILD was 41 days (range: 14 days - 702 days). For specific recommendations, refer to sections 4.2 and 4.4.

Cardiac failure
In clinical studies (N = 545), cardiac failure was reported in 4 subjects (0.7%). Two subjects (0.4%) reported cardiac failure of Grade ≥ 3. The median time-to-onset of any Grade cardiac failure was 249 days (range: 84 days – 381 days), and the median time-to-resolution was 35 days (range: 22 days – 160 days). One subject with cardiac failure died due to pulmonary oedema and upper gastrointestinal haemorrhage. Four subjects (0.7%) had a decline in LVEF of ≥ 10% to an absolute value < 50%. Nineteen subjects (3.5%) had a decline in LVEF of ≥ 15% but the absolute LVEF remained ≥ 50% in these subjects. For specific recommendations, refer to sections 4.2 and 4.4.

QTc prolongation
In clinical studies (N = 545), QT prolongation was reported in 51 subjects (9.4%) treated with Aumseqa 110 mg. In 4 subjects (0.7%) the events were Grade ≥ 3. The median time-to-onset of any Grade QT prolongation was 22 days (range: 1 day – 839 days) and the median time-to-resolution was 100 days (1 day – 1,068 days). Seven subjects (1.3%) had symptomatic events, 4 (0.7%) of which were Grade ≥ 3. The reported symptomatic events were cardiac arrest, cardio-respiratory arrest, sudden cardiac death, syncope (n = 2), and ventricular arrhythmia (n = 2 The median time-to-onset of syncope and ventricular arrhythmia was 204 days and 252 days, respectively. Two subjects with QT prolongation died: 1 due to sudden cardiac death and 1 due to cardio-respiratory arrest. 5 subjects (0.9%) had a maximum absolute QTcF interval > 500 msec and 23 subjects (4.2%) had a maximum change in QTcF from baseline > 60 msec. For specific recommendations, refer to sections 4.2 and 4.4.

Diarrhoea
In clinical studies (N = 545), diarrhoea was reported in 72 subjects (13.2%) treated with Aumseqa 110 mg. In 4 subjects (0.7%) the events were Grade ≥ 3. The median time-to-onset of any Grade diarrhoea was 27 days (range: 1 day – 1,046 days) and the median time-to-resolution was 13 days (1 day – 846 days). Three subjects (0.6%) experienced SAEs of diarrhoea. 1 subject reported potassium imbalance. Six subjects reported hypokalaemia of Grade 3. For specific recommendations, refer to section 4.2.

Elevated blood creatinine phosphokinase (CPK) and rhabdomyolysis
In clinical studies (N = 545), elevated blood CPK was reported in 173 subjects (31.7%) treated with Aumseqa 110 mg. In 41 subjects (7.5%), the events were Grade ≥ 3. The median time-to-onset of any Grade blood CPK increased was 64 days (range: 1 day – 926 days) and the median time-to-resolution

was 215 days (4 days – 1,156 days). Elevated blood CPK led to treatment discontinuation in 1 subject (0.2%). Events of elevated Blood CPK were considered rhabdomyolysis if they were Grade 3 with muscle related symptoms or Grade 4 with or without muscle related symptoms. In total, 14 subjects (2.6%) treated with Aumseqa 110 mg were considered to have experienced rhabdomyolysis. For specific recommendations, refer to sections 4.2 and 4.4.

Hepatic dysfunction
In clinical studies (N = 545), hepatic dysfunction was reported in 204 subjects (37.4%) treated with Aumseqa 110 mg. In 20 (3.7%) of these subjects the events were Grade ≥ 3. The median time-to-onset of any Grade hepatic dysfunction was 44 days (range: 1 day – 841 days) and the median time-to-resolution was 62 days (2 days – 1,036 days). AST and ALT elevations were reported in 118 (21.7%) and 110 (20.2%) subjects, respectively. Thirteen subjects (2.4%) reported AST increased of Grade ≥ 3 and 5 subjects (0.9%) reported ALT increased of Grade ≥ 3. One subject (0.2%) reported drug-induced liver injury of Grade ≥ 3 with a time-to-onset of 8 days and a time-to-resolution of 6 days. For specific recommendations, refer to sections 4.2 and 4.4.

Venous thromboembolism (VTE)
In clinical studies (N = 545), VTE (including deep vein thrombosis, pulmonary embolism, and venous thrombosis limb) was reported in 39 subjects (7.2%) treated with Aumseqa 110 mg. In 17 subjects (3.1%) the events were Grade ≥ 3. The median time-to-onset of any Grade VTE was 229 days (range: 8 days – 1,087 days) and the median time-to-resolution was 142 days (7 days – 830 days). Pulmonary embolism was reported by 21 subjects (3.9%), with 15 (2.8%) of the events being Grade ≥ 3. Venous thrombosis limb was reported by 16 subjects (2.9%), with 2 (0.4%) of the events being Grade ≥ 3. Deep vein thrombosis was reported by 9 subjects (1.7%), with 1 (0.2%) of the events being Grade ≥ 3. In addition, cerebral infarction and cerebral thrombosis were respectively reported in 4 (0.7%) and 1 (0.2%) subjects, with 3 (0.6%) of the events being Grade ≥ 3. For specific recommendations, refer to sections 4.2 and 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of accidental overdose with Aumseqa is limited. The highest dose studied was 260 mg once daily. The potential toxicity of Aumseqa at doses of 260 mg and above is unknown. The adverse reactions observed at 260 mg dose were primarily nausea and anaemia.

There is no specific treatment for Aumseqa overdose. In the event of an overdose or suspected overdose, the patient should be closely monitored, Aumseqa treatment should be withheld, and symptomatic treatment should be provided as clinically required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EB11.

Mechanism of action

Aumolertinib is an irreversible, small molecule tyrosine kinase inhibitor (TKI) of EGFR with inhibitory activity against EGFR TKI sensitising mutations (EGFR exon 19 [Ex19Del] deletion and EGFR L858R, respectively) and EGFR TKI resistance mutation (EGFR T790M). The major active metabolite of aumolertinib, HAS-719, showed a similar activity profile to aumolertinib.

Pharmacodynamic effects

Anti-proliferation activity
In vitro studies demonstrated that aumolertinib potently inhibited proliferation of EGFR T790M mutant cancer cell lines including NCI-H1975 (T790M/L858R) and PC9-GR (T790M/Del19), with IC50s of 3.3nM and 2.7nM, respectively. Aumolertinib also potently inhibited proliferation of EGFR activating mutant cancer cell lines including HCC827 (EGFR Del19) and PC9 (EGFR Del19), with IC50s of 3.3nM and 4.1nM, respectively. Aumolertinib only weakly inhibited proliferation of the EGFR wild type cancer cell line A431, with an IC50 of 596.6nM.

In vivo, aumolertinib lead to tumour shrinkage in EGFR T790M/L858R and EGFR activating mutant xenograft models in mice. In contrast, aumolertinib showed minimal tumour growth inhibition in the A431 xenograft model with the WT EGFR.

Effects on QTc interval duration

The QTc interval prolongation potential of Aumseqa was assessed in 49 subjects who received Aumseqa. Serial ECGs were collected at baseline and following a single dose and at steady-state to evaluate the effect of Aumseqa on QTc intervals. A concentration-QT analysis predicted a QTc interval prolongation at 110 mg of 9.06 msec with an upper bound of 11.01 msec (90% confidence interval [CI]).

Clinical efficacy and safety

Previously untreated EGFR mutation positive locally advanced or metastatic NSCLC subjects in the phase 3 study (HS-10296-03-01, AENEAS)

The efficacy and safety of Aumseqa for the treatment of subjects with locally advanced or metastatic NSCLC harbouring EGFR TKI-sensitising mutations, who had not received any systemic treatment, was evaluated in a randomised, double-blind, active-controlled, multicentre phase 3 clinical study (AENEAS) in China. Tumour tissue samples or blood samples[1] were required to have one of the two common EGFR mutations known to be associated with EGFR TKI sensitivity (Ex19Del and/or L858R).

A total of 429 subjects were randomised 1:1 to receive Aumseqa (110 mg once daily, n = 214) or gefitinib (250 mg once daily, n = 215). Each treatment cycle was 21 days with no gap between cycles (i.e., continuous dosing). Randomisation was stratified by EGFR mutations (Ex19Del or L858R) and the presence of baseline brain metastasis status (yes or no). Subjects continued treatment until disease progression, unacceptable risk to the patient's health or voluntary withdrawal. For patients receiving gefitinib, post-progression crossover to open-label Aumseqa was permitted, provided tumour samples tested positive for the T790M mutation.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by the investigator. The secondary endpoints included objective response rate (ORR) and duration of response (DoR).

The baseline demographic and disease characteristics in the AENEAS study for the overall population were: median age (59.3 years), ≥ 65 years (31.5%), female (62.7%), smoker (never) (69.9%), Asian (100%), tumour stage IIIB (6.8%), tumour stage IV (93.2%), tumour type: adenocarcinoma (98.1%), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 1 (74.8%), CNS metastasis (26.8%). Of the enrolled patients, 65.5% had Ex19DEL mutation, and 34.5% had L858R mutation. Overall, the demographics and disease characteristics were balanced between treatment arms.

In the primary analysis (data cut-off [DCO] 15 January 2021), Aumseqa demonstrated a statistically significant and clinically meaningful improvement in investigator-assessed PFS compared to gefitinib

[1] The cobas® EGFR Mutation Test v2 was used to identify mutations in exons 18, 19, 20, and 21 of the *EGFR* gene in tissue and plasma samples. The real-time polymerase chain reaction (PCR) test is used as a companion diagnostic to aid in selecting NSCLC subjects for treatment with EGFR tyrosine kinase inhibitors.

at the primary analysis (median 19.1 months and 9.7 months, respectively, hazard ratio (HR) = 0.46, 95%CI: 0.36, 0.59; p < 0.0001). At the time of the primary analysis, the median follow-up duration was 20.5 months in the Aumseqa group and 20.7 months in the gefitinib group.

An updated analysis was conducted with DCO date of 06 August 2021, and was consistent with the primary analysis. The median follow-up time was 26.2 months in the aumolertinib group and 26.3 months in the gefitinib group.

Table 3 presents updated data for investigator-assessed PFS, ORR, and DoR.

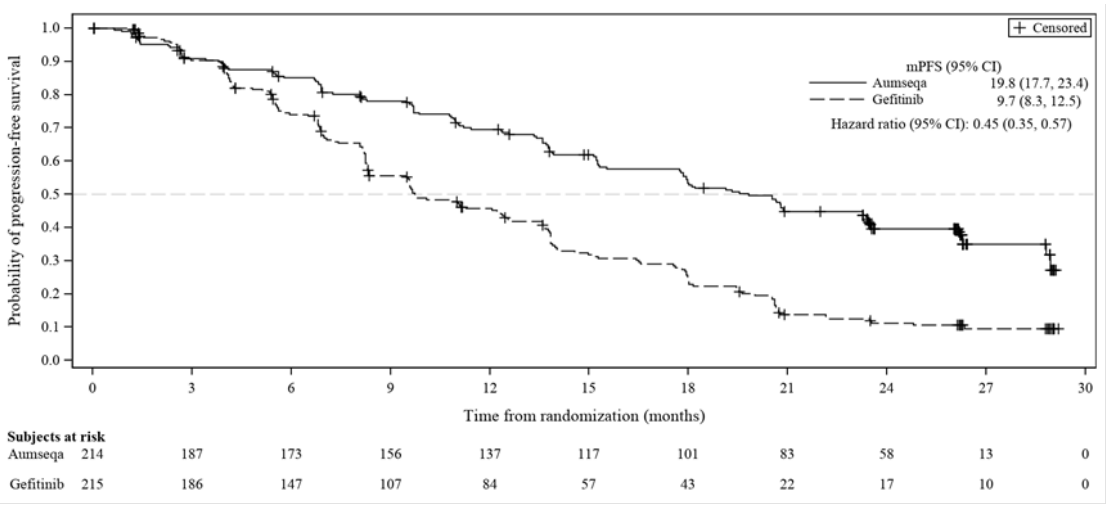
Table 3. Efficacy results from the AENEAS study by investigator assessment

Efficacy parameter	**Aumseqa**	**Gefitinib**
Progression free survival		
Number of subjects with events (%)	124 (57.9)	171 (79.5)
Median PFS in months (95% CI)	19.8 (17.7, 23.4)	9.7 (8.3, 12.5)
HR (95% CI) [1]	0.45 (0.35, 0.57)	
Objective response rate ‡		
ORR, % (95% CI)	74.8 (68.4, 80.4)	72.1 (65.6, 78.0)
Complete response (%)	1 (0.5)	1 (0.5)
Partial response (%)	159 (74.3)	154 (71.6)
Duration of response ‡		
Median DoR in months (95% CI)	19.2 (15.5, 22.1)	8.3 (6.9, 11.1)

Note: [1] Stratified cox proportional hazards model.
CI: confidence interval, HR: hazard ratio, NA: not applicable/available
‡ Data for ORR and DOR based on unconfirmed response.

Figure 1 presents a Kaplan-Meier plot of investigator-assessed PFS in the AENEAS study.

Figure 1. Kaplan-Meier estimates of investigator-assessed progression-free survival (PFS) in the AENEAS study*§



*Full analysis set (FAS)
§. Data cut-off (DCO) is 06 August 2021

In a subsequent analysis with DCO date of 30 September 2022, a total of 109 subjects (50.9%) in the aumolertinib treatment arm and 126 subjects (58.6%) in the gefitinib treatment arm had died. The median OS as of the updated DCO date was 39.16 months in the aumolertinib arm and 31.15 months in the gefitinib arm.

CNS analysis (post-hoc)
Of 429 subjects, 106 subjects (51 in the Aumseqa arm and 55 in the gefitinib arm) had baseline brain metastasis identified and confirmed by IRC. In this group of subjects, excluding 7 subjects receiving RT within 3 months initiating study treatment, the ORR was 60.4% (95% CI: 45.3, 74.2) for Aumseqa vs. 47.1% (95% CI: 32.9, 61.5) for gefitinib.

Previously treated EGFR mutation positive locally advanced or metastatic NSCLC subjects in the phase 1/2 study HS-10296-12-01 (APOLLO)

The HS-10296-12-01 (APOLLO) study, a Part 3 (dose-extension) open-label, single-arm study, evaluated the safety and efficacy of Aumseqa at the recommended dose of 110 mg once daily in subjects positive for the T790M mutation. Subjects were required to be positive for the T790M mutation by central laboratory testing[2] using a biopsy sample taken after disease progression following the most recent EGFR TKI treatment. The primary efficacy endpoint was ORR as assessed by ICR.

Subjects (n = 244) aged 27 to 87 years (median 61.0 years with 37.3% of subjects ≥ 65 years) received Aumseqa once daily. Of these, 142 (58.2%) were female and 102 (41.8%) were male; 178 (73.0%) had never smoked; 4 were active smokers (1.6%), and 62 (25.4%) had quit smoking. All the subjects' tumours had the T790M mutation, including the 155 subjects (63.5%) with an exon 19 deletion, 85 subjects (34.8%) with an L858R mutation, and 4 subjects (1.6%) with other EGFR mutations. Eighty-five subjects (34.8%) had an ECOG PS score of 0 and 159 (65.2%) had a score of 1. Ninety subjects (36.9%) had brain metastases.

The ORR assessed by IRC was 65.6% (95% CI: 59.2, 71.5) for the primary analysis. With an additional 31 months of long-term follow-up after the primary analysis, the ORR assessed by IRC was 68.9% (95% CI: 62.6, 74.6). Long-term analyses reported a median DoR of 15.1 months (95% CI: 12.9, 16.6) per IRC.

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration, aumolertinib was absorbed quickly and its median peak plasma concentration was 4 to 6 hours after single and multiple dosing. The median peak plasma concentrations of its primary active metabolite HAS-719 were observed at 4 to 6 hours post dose after multiple dosing. Aumolertinib and HAS-719 exposures (AUC) and C_{max} increased in a slightly less-than-proportional manner across the 55 to 220 mg dose range. Steady-state concentrations of aumolertinib were achieved in 8 days with approximately 1.8-fold accumulation in AUC after once daily administration. Steady-state concentrations of HAS-719 were achieved in15 days, with approximately 4.6-fold accumulation in AUC after once daily dosing of aumolertinib.

The multiple dose PK parameters of aumolertinib and HAS-719 are provided in Table 5.

[2] The cobas® EGFR Mutation Test v2 was used to identify mutations in exons 18, 19, 20, and 21 of the *EGFR* gene in tissue and plasma samples. The real-time polymerase chain reaction (PCR) test is used as a companion diagnostic to aid in selecting NSCLC subjects for treatment with EGFR tyrosine kinase inhibitors.

Table 5. Multiple dose PK parameters of aumolertinib and HAS-719 following oral administration of aumolertinib 110 mg in adults with NSCLC

Parameter*	**Aumolertinib Mean (% CV)** (N = 237)	**HAS-719 Mean (% CV)** (N = 237)
C_{max} (ng/mL)	353 (53)	118 (37)
AUC_{tau} (ng×h/mL)	6602 (53)	2468 (36)
C_{min} (ng/mL)	223 (58)	87.4 (38)

* Based on non-compartmental analysis from part 3, dose extension part, of the phase 1/2 study
AUC_{tau} = area under the plasma concentration-time curve from time zero to the endo the dosing interval, C_{max} = maximum concentration, C_{min} = lowest concentration, CV = coefficient of variation

Food effects
Based on a clinical PK study, food does not alter aumolertinib bioavailability to a clinically meaningful extent (AUC increased by 20% [90% CI: 10, 30] with no change in C_{max}).

Distribution

Based on population pharmacokinetic analysis, the apparent volume of aumolertinib distribution in subjects with NSCLC at steady-state was 875 L. *In vitro* plasma protein binding of aumolertinib and HAS-719 is high (≥ 99.5%). Aumolertinib was shown to bind both albumin and α-acidic glycoprotein with no concentration dependence at clinically relevant concentrations *in vitro*. The blood/plasma ratio of aumolertinib in humans was < 1, indicating limited partitioning into red blood cells.

Biotransformation

Aumolertinib is primarily metabolised by cytochrome P450 isozyme CYP3A4, with smaller contributions from CYP3A5, CYP1A2, and CYP2A6. HAS-719 is an active major circulating metabolite that is formed via N-demethylation.

Elimination

Following a single oral administration of a 110 mg dose of aumolertinib in humans, approximately 85% of the administered dose was eliminated in faeces as aumolertinib and its metabolites, while approximately 5% of the dose was eliminated in urine. The mean terminal half-lives of aumolertinib and HAS-719 were approximately 31 and 55 hours, respectively.

Other information on drug-drug interactions (DDI)

Interactions with transporter proteins
In vitro studies have shown that aumolertinib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, and MATE2-K.
Based on *in vitro* studies, aumolertinib did not inhibit OATP1B3, OAT3, MATE2-K, or bile salt export pump (BSEP). Aumolertinib is a weak inhibitor of organic anion transporting polypeptide (OATP)1B1, organic anion transporter (OAT)1, and OCT2 *in vitro*. Considering the C_{max} for aumolertinib following a 110 mg once daily dose, drug-drug interactions between aumolertinib and OATP1B1, OAT1, and OCT2 substrates are not anticipated to be clinically relevant.

Based on *in vitro* studies, aumolertinib is a substrate of P-gp and breast-cancer resistance proteins (BCRP).

Based on *in vitro* studies, aumolertinib is an inhibitor of BCRP, however, drug-drug interactions between aumolertinib and BCRP substrates are not anticipated to be clinically relevant based on a physiologically based pharmacokinetic (PBPK) analysis.

Interactions with drug metabolising enzymes
Based on *in vitro* studies, aumolertinib did not inhibit the major human cytochrome P450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [2 substrates]).

In vitro, aumolertinib induced CYP1A2 expression, however this effect is not anticipated to be clinically relevant. *In vitro*, aumolertinib induced CYP3A4 expression and was a time-dependent inhibitor of CYP3A. Aumolertinib decreased the exposure of midazolam (a sensitive CYP3A substrate) by approximately 27% in a clinical study, and is therefore considered a weak inducer of CYP3A (see section 4.5).

Aumolertinib was found to be an inhibitor of UGT1A1 and UGT2B7 *in vitro*. Considering the steady-state C_{max} concentrations after 110 mg daily dose, this is not likely to be clinically relevant. Intestinal interactions cannot be ruled out, however, the clinical impact is unknown.

Special population

Age, gender, body weight, and ethnicity
In a population PK analysis, no clinically significant relationships were identified between steady-state exposure (AUC_{ss}) and patient's age (range: 27 to 89 years), gender (60% female), ethnicity, and body weight (range: 37 to 106 kg).

The majority of healthy volunteers and subjects in studies to date have been of a Han Chinese ethnic background. However, data from a single dose PK bridging study in healthy volunteers found no clinically meaningful differences in aumolertinib PK between Chinese and non-Chinese subjects (including Caucasian, Black/African American and Hispanic/Latino subjects). An additional steady -state PK study in European subject with NSCLC found no clinically meaningful PK differences of aumolertinib and its metabolite HAS-719 between Chinese and non-Chinese (Caucasian) subjects.

Hepatic impairment
Hepatic metabolism is the principal route of aumolertinib clearance, and CYP3A4 is the major enzyme catalysing the biotransformation of aumolertinib. In clinical studies, C_{max} and AUC were reduced by up to 54% and 31% in subjects with moderate hepatic impairment, and by approximately 64% and 50% in subjects with severe hepatic impairment, respectively, compared to healthy controls. However, no clinically relevant changes in the exposure of unbound aumolertinib were observed in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

Based on a population PK analysis, no effect of hepatic function (as assessed by markers of liver function AST, ALT, albumin, total bilirubin, and by National Cancer Institute Organ Dysfunction Working Group [NCI-ODWG] hepatic impairment category) was identified on aumolertinib exposure.

Renal impairment
Data from the clinical studies indicate that renal clearance of aumolertinib is negligible. Consequently, it is not anticipated that aumolertinib PK will be altered by reduced renal function.

In a population PK analysis, aumolertinib and HAS-719 exposures were similar in subjects with mild renal impairment ($60 \leq CLcr < 90$ mL/min), subjects with moderate renal impairment ($30 \leq CLcr \leq 60$ mL/min), and patients with normal renal function ($CLcr \geq 90$ mL/min). Aumolertinib has not been evaluated in subjects with severe renal impairment ($CLcr < 30$ mL/min) or end-stage renal disease.

5.3 Preclinical safety data

The main findings observed in repeat dose toxicity studies in rats and/or dogs comprised effects in the skin, gastrointestinal tract, mouth, eyes, male mammary gland, liver, and lungs, which were consistent

with the pharmacology of EGFR inhibition. The observed findings provided no safety margins in relation to clinically relevant exposure. Target organ toxicities at tolerated doses were generally either completely or partially recovered during or at the end of the recovery phase of the chronic toxicity.

Non-clinical data indicate that aumolertinib and its metabolite (HAS-719) inhibit the h-ERG channel, and QTc prolonging effects cannot be excluded (see sections 4.4 and 4.8).

Carcinogenicity studies have not been conducted with aumolertinib. *In vitro* study results showed that aumolertinib is not expected to be phototoxic.

Reproductive toxicity

In a rat fertility study wherein dosing was initiated prior to implantation, decreases in mean numbers of corpora lutea, implantation sites, live fetuses were observed at 100 mg/kg along with an increase in postimplantation loss. No treatment-related changes were noted on sperm parameters. Considering also some published data reporting subfertility of mice lacking Egfr expression, female fertility may be impaired by treatment with aumolertinib. Exposure levels at the dose of 30 mg/kg shown to be devoid of effects on rat fertility is comparable to that reached in patients at the maximum recommended dose.

In an embryo-foetal development study in rats, there were no aumolertinib-related effects on embryo-foetal development at doses up to 100 mg/kg (corresponding to 3.4-fold clinical exposure at the maximum recommended human dose)

In an embryo-foetal development study in rabbits, animals received doses ranging from 5 to 30 mg/k/day which corresponded to exposure levels below (0.1- to 0.6-fold) those reached in patients at the maximum recommended dose. Maternal toxicity was observed at all dose levels. In particular, maternal death and spontaneous abortion were observed at ≥ 15 mg/kg and premature delivery occurred at 30 mg/kg. Fetal lethality was noted at all dose levels, with a decrease in the number of live fetuses at 30 mg/kg. Examination of fetuses showed treatment-related effects on fetal sternum development (decreased ossification rate at all doses and decreased number of sternebrae at ≥ 15 mg/kg), as well as an increase in an abnormality of artery arborization (at all doses).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460)
Sodium starch glycolate (type a)
Lactose
Sodium stearyl fumarate (E485)
Magnesium stearate (E572)

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original bottle in order to protect from moisture.

6.5 Nature and contents of container

White, high density polyethylene (HDPE) bottle with an aluminium heat-induction sealed child-resistant closure, a silica gel desiccant cannister inside, and a white polypropylene (PP) cap.

Each bottle contains 60 film-coated tablets.

Each carton contains one bottle.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

SFL Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Loerrach
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/25/2006/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Manufacturing Packaging Farmaca (MPF) B.V.
Neptunus 12, Heerenveen, 8448CN
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Aumseqa 55 mg film-coated tablets
aumolertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains aumolertinib mesylate equivalent to 55 mg aumolertinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not swallow the desiccant or remove it from the bottle.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original bottle in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SFL Pharmaceuticals Deutschland GmbH
79539 Loerrach
Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2006/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

aumseqa 55 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Aumseqa 55 mg film-coated tablets
aumolertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains aumolertinib mesilate equivalent to 55 mg aumolertinib.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original bottle in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SFL Pharmaceuticals Deutschland GmbH
79539 Loerrach, Germany

12. MARKETING AUTHORISATION NUMBER

EU/1/25/2006/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Aumseqa 55 mg film-coated tablets
aumolertinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Aumseqa is and what it is used for
2. What you need to know before you take Aumseqa
3. How to take Aumseqa
4. Possible side effects
5. How to store Aumseqa
6. Contents of the pack and other information

1. What Aumseqa is and what it is used for

Aumseqa contains the active substance aumolertinib, which belongs to a group of medicines called protein kinase inhibitors that are used to treat cancer. Aumseqa is used to treat adults with non-small cell lung cancer who have certain changes (mutations) in the gene coding for EGFR (epidermal growth factor receptor).

Aumseqa is used if your cancer is locally advanced or has spread to other parts of the body. It can be used:
- as the first medicine you receive for your cancer when your cancer has mutations called activating EGFR mutations , or
- if you have already been treated for your cancer with other protein kinase inhibitor medicines, and your cancer is EGFR T790M mutation-positive .

How Aumseqa works
In lung cancer cells, the EGFR protein is often overactive due to gene mutations, causing uncontrolled growth of cancer cells. Aumseqa works by blocking EGFR when it contains specific mutations. This may help to slow or stop your lung cancer from growing. It may also help reduce the size of the tumour.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take Aumseqa

Do not take Aumseqa
- if you are allergic to aumolertinib or any of the other ingredients of this medicine (listed in section 6).

- if you have or had:
  - a heart rhythm disorder, such as abnormally fast or irregular heartbeat or a condition called QT prolongation;
  - blood-related family members who have had abnormally fast or irregular heart rhythm or who died suddenly from heart problems.

Talk with your doctor if any of the above apply to you.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse before taking Aumseqa if:
- you have suffered from inflammation of your lungs;
- you have had heart problems or raised blood pressure – your doctor will keep a close eye on you;
- you have had a blood clot in a blood vessel;
- you have a history of kidney or liver disease – your doctor will conduct tests to measure how your kidney and liver work and may continue monitoring them during treatment.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist, or nurse before taking this medicine.

Tell your doctor straight away while taking this medicine if:
- you have sudden difficulty in breathing together with a cough or fever;
- you have rapid or irregular heartbeats, dizziness, light-headedness, chest discomfort, shortness of breath or faint;
- you have severe diarrhoea or vomit;
- you have unexplained muscle pain, tenderness or weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination. These could be signs that your muscles are becoming severely inflamed.

Children and adolescents
Do not give Aumseqa to children or adolescents since it is not known if Aumseqa is safe and effective in people under the age of 18 years.

Other medicines and Aumseqa
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription. This is because Aumseqa can affect the way some other medicines work. Also, some other medicines can affect the way Aumseqa works.

Aumseqa may affect how well the following medicines work and/or increase side effects of these medicines or these medicines might affect the side effects of Aumseqa. Please ask your doctor or pharmacist about the medicines you are taking, in particular:
- verapamil – used for high blood pressure and to control chest pain
- posaconazole, itraconazole, voriconazole, ketoconazole, fluconazole – used to treat fungal infection
- ritonavir, cobicistat, nelfinavir, lopinavir – used to treat human immunodeficiency virus (HIV) infection/AIDS
- clarithromycin – used to treat bacterial infection
- dabigatran – used to prevent blood clots.
- fexofenadine – used to treat allergy symptoms
- digoxin – used for irregular heartbeat or other heart problems
- colchicine – used to relieve the symptoms of gout
- nefazodone – used to treat depression.
- metformin – used to treat type 2 diabetes

The following medicines may reduce how well Aumseqa works. Please ask your doctor or pharmacist about the medicines you are taking:

- phenytoin sodium, carbamazepine, phenobarbital – used for seizures.
- rifampicin, rifabutin – used for tuberculosis and to treat bacterial meningitis.
- St. John's Wort (*Hypericum perforatum*) – a herbal medicine used for depression.
- bosentan – used for high blood pressure in the lungs.
- mitotane – used to treat Cushing disease
- efavirenz – used to treat HIV infections /AIDS.

If you are taking any of the medicines listed above, tell your doctor before taking Aumseqa.
Your doctor will discuss appropriate treatment options with you.

Aumseqa with food and drink
You should avoid drinking grapefruit juice while taking Aumseqa, because it may increase side effects.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Because there may be a risk that an unborn baby is harmed with Aumseqa, you should not become pregnant while taking this medicine.
If you are able to become pregnant, you must use effective contraception during treatment and for 4 weeks after completing treatment with Aumseqa. This is because this medicine may remain in your body for some time.
Aumseqa may interfere with how well oral hormonal contraceptives work. Discuss with your doctor the most appropriate methods of contraception.
If you do become pregnant during treatment, tell your doctor straight away. Your doctor will decide with you whether you should continue taking Aumseqa.

Breast-feeding
Do not breast-feed while taking this medicine. This is because it is not known if the medicine might pass into the milk and if there is a risk to your baby. Breast-feeding should be stopped during treatment with Aumseqa until 4 weeks after completion of treatment with Aumseqa.

Driving and using machines
Aumseqa has a small effect on the ability to drive and use machines. You may experience fatigue and dizziness. If you experience fatigue and/or dizziness, do not drive or use machines until symptoms resolve.

Aumseqa contains lactose
Aumseqa contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Aumseqa contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per daily dose, that is to say essentially "sodium free".

3. How to take Aumseqa

Always take this medicine exactly as your doctor has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

How much to take

The recommended dose is two 55 mg tablets once a day.

If necessary, your doctor may reduce your dose to one 55 mg tablet per day or temporarily stop your treatment. It is important to tell your doctor about the side effects that you are experiencing.

How to take this medicine
- Aumseqa tablets are taken by mouth.
- Swallow the tablet whole with some water. Do not crush or chew the tablets, because these tablets have been developed to be swallowed whole.
- The tablets can be taken with or without food.
- Take Aumseqa every day at approximately the same time.

Please tell your doctor, nurse, or pharmacist if you have difficulty swallowing tablets.

If you take more Aumseqa than you should
If you take more tablets than you should, tell your doctor or pharmacist straight away. You may need medical help.

If you forget to take Aumseqa
If you forget a dose, take it as soon as you remember it. However, if you need to take your next dose in less than 12 hours, skip the missed dose and take your next normal dose at its scheduled time.

Do not take a double dose (that is, 2 times 2 tablets) to make up for a forgotten dose.

If you stop taking Aumseqa
It is important to take this medicine every day, for as long as your doctor prescribes it for you.
Do not stop taking this medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

If you experience any of the following side effects stop taking the medicine and seek medical help immediately:

Common (may affect up to 1 in 10 people):
- Lung inflammation. Aumseqa can cause lung inflammation (interstitial lung disease, pneumonitis), which in some people can be fatal. Symptoms may include:
  - sudden difficulty in breathing, together with a cough and fever
  - shortness of breath at rest or made worse by exertion
  - dry cough that will not go away.

- Blood clots. Aumseqa may cause a blood clot in your lung (pulmonary embolism). Symptoms can vary greatly, and include:
  - shortness of breath
  - chest pain
  - cough with blood

  Blood clots can also form in other parts of the body. The signs and symptoms include:
  - rapid or irregular heartbeat
  - light headedness

- excessive sweating
- fever
- leg pain or swelling
- clammy skin

- Changes in heart rhythm. Aumseqa can affect the electrical activity in the heart which in some people can develop into a potentially serious heart condition. This can result in:
  - very fast or irregular heartbeat causing fainting
  - dizziness
  - light headedness
  - chest discomfort
  - shortness of breath

  The risk of heart rhythm problems may be higher for people with an existing heart condition, or who are taking other medicines.

- Muscle inflammation and muscle damage. Aumseqa can cause inflammation or breakdown of your muscle tissue, which can then lead to kidney damage. The symptoms of muscle damage include:
  - unexplained muscle pain, tenderness, or weakness,
  - trouble moving arms or legs,
  - dark tea-coloured urine,
  - or decreased urination.

Uncommon (may affect up to 1 in 100 people):

- *Heart failure or problem with your heart muscle.* Aumseqa can affect how well your heart pumps blood. Signs and symptoms include:
  - increased heart beats
  - shortness of breath at rest
  - tiredness and fatigue
  - swelling in the legs, ankles, and feet

The risk of these heart problems may be higher for people with an existing heart condition, or who are taking other medicines.

Stop taking Aumseqa and see a doctor or nurse straight away if you notice any of the serious side effects above.

Other side effects

Very common (may affect more than 1 in 10 people):

- abnormal level of liver enzymes known as aspartate aminotransferase increased (AST) and alanine aminotransferase increased (ALT) - these are normally present in blood at low levels, an increase may be a sign of unhealthy or damaged liver.
- anaemia - condition in which there are not enough healthy red blood cells to carry adequate oxygen to your body's tissues
- cough, runny nose, throat pain due to infection in the sinus, tonsils or throat
- burning sensation during urination, frequent urination, frequent urge to urinate, pain or pressure in the back or lower abdomen, blood in urine, cloudy, dark, or strange or strong-smelling urine, mixed with blood in some cases
- decreased platelet count – blood cells that help blood clot
- decreased white blood cell count – decreased disease-fighting cells
- diarrhoea
- increased blood bilirubin – an increase may be sign of an unhealthy or damaged liver.
- increased blood creatine phosphokinase (CPK), which may be a sign of muscle damage
- increased creatinine levels in the blood, which may be a sign of a kidney problem

- reduced levels of sodium or potassium in your blood, which can make you experience nausea and vomiting, headache, confusion, restlessness and irritability, muscle weakness, cramping, coma, or seizures
- mouth sores
- rash
- pruritis – an unpleasant skin sensation that provokes the desire to scratch.
- vomiting

Common (may affect up to 1 in 10 people):
- blood pressure higher than normal
- an abnormally high level of uric acid in the blood, which can cause swollen and painful joints
- decreased appetite
- dry eyes, blurred vision
- increased blood lactate dehydrogenase – may be a sign of some type of tissue damage or disease.
- elevated levels of gamma-glutamyl transferase, which might indicate liver, pancreas or kidney problem
- decreased lymphocyte count - reduction in the number of white blood cells, which can lead to reduced ability to fight infections
- nausea
- increased level of protein in the urine, which can result in foamy urine and may be a sign of a kidney problem.
- dry skin
- itchy, red skin rash
- swelling and puss around nails, thickened or discoloured nails
- bronchitis, pneumonia - infection of the lungs.
- conjunctivitis - infection of the eyes.

Uncommon (may affect up to 1 in 100 people):

- eye discomfort or foreign body sensation in the eye
- redness of the eyes
- changes to whites of the eyes that make vision unclear
- swollen eyelid(s)
- red, tender bumps on the skin
- redness, swelling, and pain on the palms of the hands and/or the soles of the feet
- pimples or pustules located around a hair or follicle

Contact your doctor or nurse if you notice any of the above side effects.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Aumseqa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after “EXP”. The expiry date refers to the last day of that month.

Do not store above 30°C.

Store in the original bottle in order to protect from moisture.

The bottle of tablets should contain a desiccant that helps keep the tablets dry. If this is missing or the aluminium seal under the cap is open or broken when opening the bottle for the first time, please contact your pharmacist who will advise you on what to do.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Aumseqa contains

- The active substance is aumolertinib. Each film-coated tablet contains aumolertinib mesylate equivalent to 55 mg of aumolertinib.
- The other ingredients are microcrystalline cellulose (E460), sodium starch glycolate (type a), lactose, sodium stearyl fumarate (E485), magnesium stearate (E572), polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350, talc (E553b), and iron oxide yellow (E172) (see section 2).

What Aumseqa looks like and contents of the pack
The film-coated tablets are 7 mm round, biconvex, yellow, debossed with “E1” on one side and plain on the reverse.

Each carton contains one plastic bottle with 60 film-coated tablets and a desiccant. Do not swallow the desiccant. Do not remove it from the bottle.

Marketing Authorisation Holder
SFL Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Loerrach
Germany

Manufacturer
Manufacturing Packaging Farmaca (MPF) B.V.
Neptunus 12, Heerenveen, 8448CN
The Netherlands

This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu and on the website of Germany.