PROFFESIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Alecensa® 150 mg (Hard capsule)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains alectinib 150 mg equivalent to 161,3 mg alectinib hydrochloride.

Excipients with known effect: Lactose monohydrate.

Contains sugar, lactose monohydrate 33,67 mg (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Alecensa hard capsules are white to yellowish white, size 1 capsules with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on the body.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Alecensa is indicated for first-line monotherapy treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic adenocarcinoma of the lung.

Alecensa is indicated for monotherapy treatment of adult patients with ALK-positive, locally advanced or metastatic NSCLC who have progressed on or are intolerant to crizotinib.

4.2 Posology and method of administration

Posology

The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally, twice daily (total daily dose of 1 200 mg) (see section 5.2).

Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg) (see Special Dosing Instructions and section 5.2, Pharmacokinetics in Special Populations).

Duration of Treatment

It is recommended that patients are treated with Alecensa until disease progression or unmanageable toxicity.

Delayed or Missed Doses

If a planned dose of Alecensa is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of Alecensa, patients should take the next dose at the scheduled time.

Dose Modifications

Management of adverse events may require temporary interruption, dose reduction, or discontinuation of treatment with Alecensa. The dose of Alecensa should be reduced in steps of 150 mg twice daily based on tolerability. Alecensa treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Table 1 below gives general dose modification advice for Alecensa.

Table 1 Dose Reduction Schedule

Dose reduction schedule	*Dose level*
Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

Table 2 Dose modification advice for specified Adverse Drug Reactions (see sections 4.4 and 4.8):

Grade	**Alecensa Treatment**

Interstitial Lung Disease (ILD)/Pneumonitis (all Grades)	Immediately interrupt and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified
ALT or AST elevation of Grade ≥3 (> 5 times ULN) with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ Grade 1 (≤ 3 times ULN), then resume at reduced dose (see Table 1)
ALT or AST elevation of Grade ≥ 2 (> 3 times ULN) with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis	Permanently discontinue Alecensa
Bradycardia[a] Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose (see Table 1)

	upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia[a] Grade 4 (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm, with frequent monitoring as clinically indicated. Permanently discontinue in case of recurrence.
CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2,5 times ULN, then resume at same dose
CPK elevation >10 times ULN or second occurrence of CPK elevation of > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2,5 times ULN, then resume at reduced dose as per Table 1
Haemolytic anaemia with haemoglobin of < 10 g/dL (Grade ≥ 2)	Temporarily withhold until resolution, resume at reduced dose (see Table 1) or permanently discontinue.

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal [a] Heart rate less than 60 beats per minute (bpm)

Special Dosage Instructions

Paediatric use

The safety and efficacy of Alecensa in children and adolescents (<18 years) have not been studied.

Geriatric use

No dose adjustment of Alecensa is required in patients ≥ 65 years of age.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Alecensa has not been studied in patients with severe renal impairment, however since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment (see section 5.2, Pharmacokinetics in Special Populations).

Hepatic Impairment

No dose adjustment is required in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg) (see section 5.2, Pharmacokinetics in Special Populations).

Method of Administration

Precautions to be taken before manipulating or administering Alecensa.

A validated ALK assay is required for the selection of ALK-positive NSCLC patients. ALK-positive NSCLC status should be established prior to initiation of Alecensa therapy.

Alecensa hard capsules should be taken with food, swallowed whole and must not be opened or dissolved.

4.3 Contraindications

Alecensa is contraindicated in patients with a known hypersensitivity to alectinib or any of the excipients.

Pregnancy and lactation. See section 4.6.

4.4 Special warnings and precautions for use

General

Interstitial lung disease (ILD)/Pneumonitis

Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa (see section 4.8). Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alecensa

should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified (see section 4.2).

Hepatotoxicity

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 5 times the upper limit of normal (ULN) as well as bilirubin elevations of more than 3 times the ULN occurred in patients in pivotal clinical trials with Alecensa (see section 4.8). The majority of these events occurred during the first 3 months of treatment. In the pivotal Alecensa clinical trials there were reports of Grade 3-4 AST/ALT elevations with medicine induced liver injury. Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, may occur.

Liver function, including ALT, AST, and total bilirubin should be monitored at baseline and then every 2 weeks during the first 3 months of treatment, and then periodically, since events may occur later than 3 months, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold Alecensa and resume at a reduced dose, or permanently discontinue Alecensa as described in Table 2 (see section 4.2).

Severe Myalgia and Creatine Phosphokinase (CPK) elevation

Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alecensa, including Grade 3 events.

Elevations of CPK occurred in pivotal trials with Alecensa, including Grade 3 events. Median time to Grade 3 CPK elevation was 14 - 27,5 days in the pivotal trials (see section 4.8).

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, withhold Alecensa, then resume or reduce dose (see section 4.2).

Bradycardia

Symptomatic bradycardia can occur with Alecensa see section 4.2.

Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia (see section 4.2). If patients experience symptomatic bradycardia or life-threatening events, concomitant medications known to cause bradycardia, as well as anti-hypertensive medications should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (see sections 4.2 and 4.5).

Haemolytic anaemia

Haemolytic anaemia has been reported with Alecensa (see section 4.8 Postmarketing Experience). If haemoglobin concentration is below 10 g/dL and haemolytic anaemia is suspected, withhold Alecensa and initiate appropriate laboratory testing. If haemolytic anaemia is confirmed, resume at a reduced dose upon resolution or permanently discontinue Alecensa (see section 4.2).

Photosensitivity

Photosensitivity to sunlight has been reported with Alecensa administration (see section 4.8). Patients should be advised to avoid prolonged sun exposure while taking Alecensa and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad-spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sun screen and lip balm (SPF ≥ 50) to help protect against potential sunburn.

Embryo-foetal toxicity

Alecensa may cause foetal harm when administered to a pregnant woman. When administrated to pregnant rats and rabbits, alectinib caused embryo-foetal toxicity. Female patients of child-bearing potential, or women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa (see section 4.6, Use in Special Populations).

Sugars

Alecensa contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take Alecensa.

4.5 Interaction with other medicines and other forms of interaction

Effects of alectinib on others medicines

CYP substrates

In vitro studies indicate that neither alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib and M4 show weak time-dependent inhibition of CYP3A4. *In vitro*, alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Results from a clinical drug-drug interaction study in ALK-positive NSCLC patients demonstrated that multiple doses of alectinib had no influence on the exposure of midazolam, a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.

Although *in vitro* studies indicate that alectinib is an inhibitor of CYP2C8, physiologically based pharmacokinetic (PBPK) modelling supports that at clinically relevant concentrations alectinib does not have the potential to increase plasma concentrations of co-administered substrates of CYP2C8.

P-gp and BCRP substrates

In vitro, alectinib and M4 are inhibitors of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Therefore, alectinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP transporters (the increase in exposure is not expected to be more than 2-fold). When alectinib is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate), appropriate monitoring is recommended.

Effects of other medicines on alectinib

Based on *in vitro* data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4, and CYP3A contributes to 40 % - 50 % of total hepatic metabolism. M4 has shown similar *in vitro* potency and activity to alectinib against ALK.

CYP3A inducers

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib exhibited a minor effect on combined exposure of alectinib and M4 (geometric mean ratio with/without rifampicin [90 % confidence interval]: C_{max}: 0,96 [0,88 – 1,05], AUC_{inf}: 0,82 [0,74 – 0,90]). Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inducers.

CYP3A inhibitors

Co-administration of multiple oral doses of 400 mg posaconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib had a minor effect on combined exposure of alectinib and M4 (geometric mean ratio with/without posaconazole [90 % confidence interval]: $C_{max:}$ 0,93 [0,81 – 1,08], AUC_{inf}: 1,36 [1,24 – 1,49]). Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inhibitors.

Medicines that increase gastric pH

Although the aqueous solubility of alectinib *in vitro* is pH dependent, a dedicated clinical drug-drug interaction study with 40 mg esomeprazole once daily, a proton pump inhibitor, demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when Alecensa is co-administered with proton pump inhibitors or other drugs which raise gastric pH (e.g. H2 receptor antagonists or antacids).

Effect of transporters on alectinib disposition

Based on *in vitro* data, alectinib is not a substrate of P-gp. Alectinib and M4 are not substrates of BCRP or Organic anion-transporting polypeptide (OATP) 1B1/B3. In contrast, M4 is a substrate of P-gp. Alectinib inhibits P-gp, and therefore, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 exposure.

4.6 Fertility, pregnancy and lactation

Use in Special Populations

Females and Males of Reproductive Potential

Contraception

Female patients of child-bearing potential, or women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa.

Pregnancy

Alecensa is contraindicated during pregnancy. (See section 4.3).

Based on its mechanism of action, Alecensa may cause foetal harm when administered to a pregnant woman. In animal studies, alectinib caused embryo-foetal toxicity.

Female patients or women who are partners of male patients receiving Alecensa, who become pregnant while taking Alecensa or during the 3 months following the last dose of Alecensa must contact their doctor and should be advised of the potential harm to the foetus.

Lactation

Alecensa is contraindicated in mothers who are breastfeeding their infants.

4.7 Effects on ability to drive and use machines

Several side effects may impair the patients' ability to drive or use machines eg. vision disturbances and bradycardia. (see section 4.8)

4.8 Undesirable effects

Clinical Trials

For the clinical development program of Alecensa as a whole, an estimated total of 928 patients have received Alecensa and 203 patients have received blinded Alecensa. The safety of Alecensa has been evaluated in 253 patients in pivotal phase II clinical trials treated with the recommended dose of 600 mg twice daily. The median duration of exposure to Alecensa was

11 months (range 0-35 months). The safety of Alecensa was also evaluated in 152 patients with ALK-positive NSCLC treated with a dose of 600 mg twice daily in the phase III clinical trial. The median duration of exposure to Alecensa was 17,9 months.

The most common adverse drug reactions (≥ 20 %) were constipation (36 %), oedema (34 % including peripheral, generalised, eyelid, periorbital); myalgia (31 % including myalgia and musculoskeletal pain), nausea (22 %), increased bilirubin (21 % including increased blood bilirubin, hyperbilirubinaemia and increased conjugated bilirubin), anaemia (20 %, including anaemia and decreased haemoglobin), and rash (20 %, including rash, maculopapular rash, acneiform dermatitis, erythema, generalised rash, papular rash, pruritic rash and macular rash).

Table 3 lists the adverse drug reactions (ADRs) occurring in patients who received Alecensa in clinical trials. Adverse drug reactions from clinical trials are listed by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 3 – Adverse drug reactions occurring in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673) and phase III trial BO28984

Adverse Reactions (MedDRA)	**Alecensa N=253 (NP28761, NP28673) /N=152 (BO28984)**		
System Organ Class	**All Grades (%)**	**Grade 3 – 4 (%)**	**Frequency Category (All Grades)**
Gastrointestinal Disorders			
Constipation	36	0	very common
Nausea	22	0,7	very common
Diarrhoea	18	1,2	very common
Vomiting	13	0,4	very common

Stomatitis	3,3	0	common
General Disorders and Administration Site Conditions			
Oedema	34	0,8	very common
Musculoskeletal and Connective Tissue Disorders			
Myalgia	31	1,2	very common
Increased Blood Creatine Phosphokinase	13	3,6	very common
Skin and Subcutaneous Tissue Disorders			
Rash	20	0,7	very common
Photosensitivity Reaction	12	0,7	very common
Nervous System Disorders			
Dysgeusia	3,3	0,7	common
Hepatobiliary Disorders			
Increased Bilirubin	21	3,3	very common
Increased AST	16	5,3	very common
Increased ALT	15	4,6	very common
Drug-Induced Liver Injury	0,8	0,8	uncommon
Blood and Lymphatic System Disorders			
Anaemia	20	4,6	very common
Eye Disorders			
Vision Disorders	12	0	very common
Cardiac Disorders			
Bradycardia	11	0	very common
Investigations			
Increased Weight	9,9	0,7	common
Renal and Urinary Disorders			

Increased Blood Creatinine	7,9	1,3	common
Acute kidney injury	2,6	2,6	common
Respiratory, Thoracic and Mediastinal Disorders			
Interstitial Lung Disease/ Pneumonitis	1,3	0,4	common

Further information on selected adverse drug reactions:

The safety profile of Alecensa was generally consistent across the phase III clinical trial and the pivotal phase II trials; however, relevant differences between studies are described below.

Interstitial Lung Disease (ILD)/pneumonitis

Severe ILD/pneumonitis occurred in patients treated with Alecensa. In the pivotal phase II clinical trials, 1 out of 253 patients treated with Alecensa (0,4 %) had an ILD event, which was Grade 3, leading to withdrawal from Alecensa treatment. There were no fatal cases of ILD in any of the clinical trials.

Hepatotoxicity

In the pivotal phase II clinical trials two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. Adverse reactions of increased AST and ALT levels (16 % and 14 % respectively) were reported in patients treated with Alecensa in pivotal phase II clinical trials. The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 2,8 % and 3,2 % of the patients, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (reported for 1,2 % and 3,2 % of the patients, respectively) or dose reduction (1,6 % and 0,8 %, respectively). In 1,2 % and 1,6 % of the patients, AST and ALT elevations, respectively, led to withdrawal from Alecensa treatment.

Adverse reactions of bilirubin elevations were reported in 17 % of the patients treated with Alecensa in pivotal phase II clinical trials. The majority of the events were of Grade 1 and 2

intensity; Grade 3 events were reported in 3,2 % of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (4,7 % of the patients) or dose reduction (2,8 %). In 4 patients (1,6 %), bilirubin elevations led to withdrawal from Alecensa treatment.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in 1 patient treated in Alecensa clinical trials.

Bradycardia

Cases of bradycardia (7,9 %) have been reported in patients treated with Alecensa in pivotal phase II clinical trials; all cases were of Grade 1 or 2 intensity. There were 44 of 221 patients (20 %) treated with Alecensa who had post-dose heart rate values below 50 beats per minutes [bpm].

Severe Myalgia and CPK elevation

Cases of myalgia (31 %) including myalgia events (25 %) and musculoskeletal pain (7,5 %) have been reported in patients treated with Alecensa in pivotal phase II clinical trials. The majority of events were Grades 1 or 2 and three patients (1,2 %) had a Grade 3 event. Dose modifications due to these events were only required for two patients (0,8 %). Elevations of CPK occurred in 46 % of 219 patients with CPK laboratory data available in pivotal phase II clinical trials with Alecensa. The incidence of Grade 3 elevations of CPK was 5,0 %. Median time to Grade 3 CPK elevation was 14 days in the pivotal phase II trials. Median time to Grade 3 CPK elevation was 27,5 days in the pivotal phase III clinical trial. Dose modifications for elevation of CPK occurred in 4,0 % of patients.

Laboratory Abnormalities

The following table displays treatment-emergent shifts in laboratory abnormalities occurring in patients treated with Alecensa in phase II clinical trials and phase III trial.

Table 4 Alecensa Treatment-emergent shifts in key laboratory abnormalities

Parameter	**Alectinib N= 250*/N=152**	
	All Grade (%)	**Grade 3 -4(%)**
Chemistry		
Increased Blood Creatinine**	38	3,4
Increased AST	53*	6,2
Increased ALT	40	6,1
Increased Blood Creatine Phosphokinase	46*	5,0*
Increased Blood Bilirubin	53	5,5
Haematology		
Decreased Haemoglobin	62	6,8

AST - Aspartate Aminotransferase, ALT - Alanine Aminotransferase

Note: Laboratory abnormalities were based on the normal ranges of the NCI CTCAE.

* Rate reported in NP28761 and NP28673 studies, N= 219 for Creatine Phosphokinase.

** Only patients with creatinine increases based on ULN definition (CTCAE grading).

Post marketing Experience

The adverse drug reaction of increased alkaline phosphatase was reported with Alecensa in the post marketing period. Cases of increased alkaline phosphatase have been reported in Alecensa clinical trials (7,5 % in patients treated with Alecensa in pivotal phase II clinical trials.

The adverse drug reaction of haemolytic anaemia was reported with Alecensa in the post marketing setting. Cases of haemolytic anaemia have been reported in the Alecensa clinical trial (BO29554).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are

asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Patients who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with Alecensa.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent protein kinase inhibitor, ATC code: L01ED03.

Mechanism of Action: Alectinib is an anaplastic lymphoma kinase (ALK) and rearranged during transfection (RET) tyrosine kinase inhibitor. In non-clinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including STAT 3 and PI3K/AKT and induces tumour cell death (apoptosis).

Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4) has shown similar *in vitro* potency and activity.

Based on non-clinical data, alectinib is not a substrate of p-glycoprotein (P-gp) or Breast Cancer Resistance Protein (BCRP), which are both efflux transporters in the blood brain barrier, and is therefore able to distribute into and be retained within the central nervous system.

5.2 Pharmacokinetic properties

The pharmacokinetic parameters for alectinib and its major active metabolite (M4), have been characterised in ALK-positive NSCLC patients and healthy subjects. The geometric mean (coefficient of variation %) steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for alectinib were approximately

665 ng/mL (44,3 %), 572 ng/mL (47,8 %) and 7430 ng*h/mL (45,7 %), respectively. The geometric mean steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for M4 were approximately 246 ng/mL (45,4 %), 222 ng/mL (46,6 %) and 2810 ng*h/mL (45,9 %), respectively.

Absorption

Following oral administration of 600 mg twice daily under fed conditions in ALK-positive NSCLC patients, alectinib was absorbed with a T_{max} of 4 to 6 hours.

Alectinib steady-state was reached by Day 7 with continuous 600 mg twice daily dosing and remained-stable thereafter. The geometric mean accumulation ratio estimated by population PK analysis for the twice-daily 600 mg regimen was 5,6. Population PK analysis supported dose proportionality for alectinib across the dose range of 300 to 900 mg under fed conditions.

The absolute bioavailability of alectinib was 36,9 % (90 % CI: 33,9 %, 40,3 %) under fed conditions in healthy subjects.

Following a single oral administration of 600 mg with a high-fat, high-calorie meal, exposure increased by 3-fold relative to fasted conditions (geometric mean ratio [90 % CI] of combined alectinib and M4: Cmax: 3,31 [2,79 – 3,93], AUCinf: 3,11 [2,73 – 3,55].

Distribution

Alectinib and its major metabolite M4 are highly bound to human plasma proteins (>99 %), independent of drug concentration. The mean *in vitro* human blood-to-plasma concentration ratios of alectinib and M4 are 2,64 and 2,50, respectively, at clinically relevant concentrations.

The geometric mean volume of distribution at steady state (V_{ss}) of alectinib following IV administration was 475 L, indicating extensive distribution into tissues.

Metabolism

In vitro metabolism studies showed that CYP3A4 is the main CYP isozyme mediating alectinib and its major metabolite M4 metabolism, and is estimated to contribute 40-50 % of alectinib metabolism in human hepatocytes.

Results from the human mass balance study demonstrated that alectinib and M4 were the main circulating moieties in plasma with alectinib and M4 together constituting approximately 76 % of

the total radioactivity in plasma. The geometric mean Metabolite/Parent ratio at steady state is 0,399.

Elimination

Following administration of a single dose of ^{14}C-labeled alectinib administered orally to healthy subjects the majority of radioactivity was excreted in faeces (mean recovery 97,8 %, range 95,6 %-100 %) with minimal excretion in urine (mean recovery 0,46 %, range 0,30 %-0,60 %). In faeces, 84 % and 5,8 % of the dose was excreted as unchanged alectinib or M4, respectively. Based on a population PK analysis, the apparent clearance (CL/F) of alectinib was 81,9 L/hour. The geometric mean of the individual elimination half-life estimates for alectinib was 32,5 hours. The corresponding values for M4 were 217 L/hour and 30,7 hours, respectively.

Pharmacokinetics in special populations:

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of alectinib in this population.

Geriatric population

Age does not have an effect on alectinib exposure.

Renal impairment

Negligible amounts of alectinib and the active metabolite M4 are excreted unchanged in urine (< 0,2 % of the dose). Data obtained in patients with mild and moderate renal impairment show that the pharmacokinetics of alectinib are not significantly affected in renal impairment. No formal pharmacokinetic study has been conducted and no population PK data was collected in patients with severe renal impairment, however since alectinib elimination via the kidney is negligible no dose adjustment is required in renal impairment.

Hepatic impairment

As elimination of alectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of alectinib and/or its major active metabolite M4. Based on a population pharmacokinetic analysis, alectinib and M4 exposures were similar in patients

with mild hepatic impairment (baseline total bilirubin less than or equal to ULN and baseline AST greater than ULN or baseline total bilirubin greater than 1,0 to 1,5 times ULN and any baseline AST) and normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN).

Following administration of a single oral dose of 300 mg alectinib in subjects with moderate (Child-Pugh B) hepatic impairment the combined exposure of alectinib and M4 was modestly increased compared with matched healthy subjects (geometric mean ratio [90 % confidence interval] for moderate/healthy: $C_{max:}$ 1,16 [0,786 – 1,72], AUC_{inf}: 1,36 [0,947 – 1,96]). Administration of a single oral dose of 300 mg alectinib in subjects with severe (Child-Pugh C) hepatic impairment resulted in a greater increase in the combined exposure of alectinib and M4 compared with matched healthy subjects (geometric mean ratio [90 % confidence interval] for severe/healthy: $C_{max:}$ 0,981 [0,517 – 1,86], AUC_{inf}: 1,76 [0,984 – 3,15]).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carboxymethycellulose calcium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulphate.

The capsule shell contains carnauba wax, carrageenan, corn starch, hypromellose, potassium chloride, titanium dioxide (E171).

The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD and C Blue 2 (aluminium lake, E132), carnauba wax, white shellac, glyceryl monooleate, 1-butanol and dehydrated ethyl alcohol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Keep in the outer carton, in order to protect from light and moisture, until required for use.

Keep out of reach of children.

Do not use after the expiry date (EXP) shown on the pack.

6.5 Nature and contents of container

Alecensa hard capsules are packaged in aluminium foil push-through blisters consisting of three-layered oriented polyamide/aluminium/polyvinyl chloride film and hard-tempered aluminium foil. Each multipack pack contains 224 capsules of 4 individual packs each containing 56 capsules (7 x blisters of 8 capsules each).

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

53/32.16/0183

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 01 March 2022

10. DATE OF REVISION OF THE TEXT

Last revision: 25 August 2022

APPROVED MANUFACTURER(S)

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