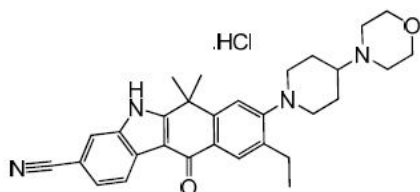


## NAME OF THE MEDICINE

# ALECENSA®

*Alectinib hydrochloride*

CAS: 1256589-74-8



## DESCRIPTION

ALECENSA (alectinib hydrochloride) is a tyrosine kinase inhibitor for oral administration. The molecular formula is  $C_{30}H_{35}ClN_4O_2$  HCl. The molecular weight is 482.62 g/mol (free base form) and 519.08 g/mol (hydrochloride salt). Alectinib hydrochloride is described chemically as: 9-ethyl-6,6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6,11-dihydro-5H-benzo[*b*]carbazole-3-carbonitrile hydrochloride. Alectinib HCl is a white to yellow white powder or powder with lumps, with a pKa of 7.05 (base). It has low solubility in aqueous buffers across the pH range, and low to high solubility in organic solvents.

ALECENSA is available as a hard capsule which contains 161.3 mg alectinib HCl equivalent to 150 mg alectinib. ALECENSA capsules also contain the following excipients: lactose monohydrate, hypromellose, sodium lauryl sulfate, carmellose calcium and magnesium stearate. The capsule shell contains carrageenan, potassium chloride, titanium dioxide, carnauba wax, maize starch and hypromellose. The capsule black printing ink includes iron oxide red, iron oxide yellow, indigo carmine aluminium lake, carnauba wax, shellac and glyceryl monooleate.

## PHARMACOLOGY

### *Mechanism of action*

Alectinib is a tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK) and Rearranged during Transfection (RET) tyrosine kinase.

In preclinical studies, alectinib inhibits ALK tyrosine kinase activity, leading to blockage of downstream signalling pathways including STAT3 and PI3K/AKT, and inhibits proliferation of cancer cells harbouring ALK fusion proteins.

Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of ALK, including some that have been identified in non-small cell lung cancer (NSCLC) tumours in patients who progressed on crizotinib. The major active metabolite of alectinib (M4) showed similar *in vitro* potency and activity.

Administration of alectinib to mice implanted with ALK-rearranged tumour cell line xenografts, including some that received intracranial xenografts, resulted in antitumour activity and prolonged survival.

### ***Pharmacokinetics***

The pharmacokinetic (PK) parameters for alectinib and its major active metabolite (M4) have been characterised in healthy subjects and in patients with ALK-positive NSCLC. The results for patients with ALK-positive NSCLC are summarised in Table 1.

**Table 1. Steady-state PK seen with recommended 600 mg twice daily dosing of alectinib [cited as geometric mean (coefficient of variation %)]**

<b>PK parameter</b>	<b>Alectinib</b>	<b>M4</b>
Maximal concentration (C <sub>max</sub> )	665 ng/mL (44.3%)	246 ng/mL (45.4%)
Trough concentration (C <sub>min</sub> )	572 ng/mL (47.8%)	222 ng/mL (46.6%)
Area under the curve from 0-12 hours (AUC <sub>0-12</sub> )	7430 ng*h/mL (45.7%)	2810 ng*h/mL (45.9%)

### ***Absorption***

The absolute bioavailability of alectinib was 36.9% (90% CI: 33.9%, 40.3%) under fed conditions in healthy subjects.

Alectinib reached maximal serum concentrations 4 to 6 hours post-dose when administered orally at 600 mg twice daily under fed conditions to patients with ALK-positive NSCLC. For both alectinib and M4, steady-state concentrations were reached by Day 7.

Population PK analysis estimated geometric mean accumulation ratio to be 6-fold for both alectinib and M4, and supports that alectinib exposure is dose proportional across the dose range 300 mg to 900 mg under fed conditions.

A high-fat, high-calorie meal increased the combined exposure of alectinib and M4 by 3-fold (AUC<sub>0-inf</sub> 3.1 [90% CI: 2.7, 3.6]) relative to fasted conditions following oral administration of a single 600 mg dose of alectinib.

### ***Distribution***

Alectinib and 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<sub>ss</sub>) of alectinib following IV administration was 475 L, indicating extensive distribution into tissues.

Alectinib is not an *in vitro* substrate of efflux transporters p-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, or OATP1B3. The same is true for M4, except that M4 is a substrate of P-gp. Alectinib concentrations in the cerebrospinal fluid of patients with ALK-positive NSCLC were similar to the estimated free alectinib concentrations in their plasma.

### ***Metabolism***

*In vitro* studies showed that alectinib is mainly metabolised by cytochrome p450 (CYP) isozyme CYP3A4 (40-50% of alectinib metabolism in human hepatocytes) to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.40.

M4 is subsequently metabolised by CYP3A4. Results from a human mass balance study utilising <sup>14</sup>C-labeled alectinib demonstrated that alectinib and M4 are the main circulating moieties in plasma, constituting 76% of the total radioactivity.

### ***Excretion***

Following administration of a single oral dose of <sup>14</sup>C-labeled alectinib to healthy subjects, the majority of radioactivity was excreted in faeces (mean recovery 97.8%, range 95.6%-100%). Most of the dose (84%) was excreted as unchanged alectinib with 6% excreted as M4. There was minimal excretion in urine (mean recovery 0.46%, range 0.30%-0.60%).

Based on a population PK analysis, the apparent clearance (CL/F) was 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life was 32.5 hours for alectinib and 30.7 hours for M4 in patients with ALK-positive NSCLC.

### ***Pharmacokinetics in Special Populations***

Population PK analysis of data from two Phase I/II clinical trials (Study 1 and Study 2) was undertaken to characterise the PK of alectinib and M4 in special populations.

#### ***Effects of age, body weight, sex and race***

In the range of exposure achieved with the 600 mg twice daily dose, age, body weight, race and sex had no clinically meaningful effect on the systemic exposure of alectinib and M4. The pharmacokinetics of alectinib has not been studied in children.

#### ***Hepatic impairment***

Mild hepatic impairment had no clinically meaningful effect on the systemic exposure of alectinib and M4. No dose adjustment is required in mild hepatic impairment. Mild hepatic impairment is defined as baseline total bilirubin (Br) ≤ the upper limit of normal (ULN) and baseline aspartate aminotransferase (AST) > ULN or baseline total Br > 1.0 to 1.5 times ULN and any baseline AST. Elimination of alectinib is predominantly through hepatic metabolism, and the pharmacokinetics of alectinib has not been studied in patients with moderate to severe hepatic impairment.

#### ***Renal impairment***

Mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min) had no clinically meaningful effect on the systemic exposure of alectinib and the active metabolite M4. No dose adjustment is required in mild to moderate renal impairment. Negligible amounts of alectinib and M4 are excreted unchanged in urine (<0.2% of the dose). The pharmacokinetics of alectinib has not been studied in patients with severe renal impairment, however due to the negligible renal clearance of alectinib, no dose adjustment is required in severe renal impairment.

#### ***Other***

Alectinib absorbs UV light between 200 and 400 nm and demonstrated phototoxic potential in an *in vitro* photosafety test in cultured murine fibroblasts after UVA irradiation.

## **CLINICAL TRIALS**

*ALECENSA is approved as monotherapy on the basis of overall response rate and duration of response rate from two single-arm, open-label, multicentre Phase I/II clinical trials. A condition of approval is the submission when available of the study report for a Phase III study (already underway) designed to provide further efficacy and safety data.*

The use of ALECENSA in the treatment of ALK-positive NSCLC patients previously treated with crizotinib was investigated in two multicentre, open-label, single-arm studies, referred to in this document as Study 1 and Study 2. Both studies enrolled patients with locally advanced or metastatic ALK-positive NSCLC, who had progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG performance status of up to 2. Eligibility criteria permitted enrolment of patients with prior chemotherapy and prior CNS radiotherapy provided that CNS metastases were stable for at least two weeks.

All patients received ALECENSA 600 mg orally twice daily. The primary endpoint in both studies was objective response rate (ORR) in the overall population, according to Response Evaluation Criteria in Solid Tumours (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional outcome measures as evaluated by the IRC included duration of response (DOR), CNS ORR, and CNS DOR. Study 2 included as co-primary endpoint evaluation of ORR by IRC using RECIST v1.1 in patients with prior exposure of cytotoxic chemotherapy treatments.

Study 1 was conducted in North America and included 87 patients in the Phase II part of the study. Baseline demographic and disease characteristics in Study 1 were median age 54 years (range 29 to 79 years, 18% ≥ 65 years), 84% White and 8% Asian, 55% female, 35% ECOG performance status 0 and 55% ECOG performance status 1, 100% never or former smokers, 99% Stage IV, 94% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 60% CNS (of whom 65% had received CNS radiation), 43% lymph nodes, 36% bone, and 34% liver.

Study 2 was conducted internationally and included 138 patients in the Phase II part of the study. Baseline demographic and disease characteristics in Study 2 were median age 52 years (range 22 to 79 years, 10% ≥ 65 years), 67% White and 26% Asian, 56% female, 32% ECOG performance status 0 and 59% ECOG performance status 1, 98% never or former smokers, 99% Stage IV, 96% adenocarcinoma, and 80% prior chemotherapy. The most common sites of extra-thoracic metastasis included 61% CNS (of whom 73% had received CNS radiation), 51% bone, 38% lymph nodes, and 30% liver.

### ***Efficacy***

Efficacy results from Studies 1 and 2 in all treated patients are summarised in Table 2. The median duration of follow-up was 17 months in Study 1 and 21 months in Study 2 for both IRC and Investigator assessments. According to the IRC, all responses were partial responses. According to Investigator assessment, 2 patients and 3 patients achieved a complete response in Study 1 and Study 2, respectively.

**Table 2. Efficacy results in Studies 1 and 2 (ITT population)**

<b>Efficacy Parameter</b>	<b>Study 1<sup>1</sup></b>		<b>Study 2<sup>2</sup></b>	
	<b>IRC*</b>	<b>Investigator</b>	<b>IRC*</b>	<b>Investigator</b>
<b>ORR in ITT population</b>	n=87	n=87	n=138	n=138
(95% CI)	42.5%	52.9%	44.9%	51.4%
Number of responders	(32.0; 53.6)	(41.9; 63.7)	(36.5; 53.6)	(42.8; 60.0)
	37	46	62	71
<b>ORR in patients pre-treated with chemotherapy</b>	n/a	n/a	n=110 39.1%	n=110 50.0%

**Attachment 1: Product information for AusPAR Alecensa Alecnic hydrochloride Roche Products Pty Limited PM-2015-04677-1-4 Final 27 November 2017. This Product Information was approved at the time this AusPAR was published.**

Efficacy Parameter (95% CI)	Study 1 <sup>1</sup>		Study 2 <sup>2</sup>	
	IRC*	Investigator	IRC*	Investigator
Number of responders			(29.9; 48.9) 43	(40.3; 59.7) 55
<b>Median DOR (months) in ITT population</b> (95% CI)	n=37 14.9 (7.5; NE)	n=46 13.3 (8.8; 18.2)	n=62 15.2 (11.2; 24.9)	n=71 13.7 (11.0; 20.3)

<sup>1</sup> Data cutoff date: 22-Jan-2016    <sup>2</sup> Data cutoff date: 01-Feb-2016

ITT=intent-to-treat; CI=confidence interval; IRC=independent review committee; n/a=not applicable; NE=not estimable; ORR=objective response rate; DOR=duration of response

\* 20 patients in Study 1 and 16 patients in Study 2 did not have measurable disease at baseline as per IRC assessment and could only be classified as a responder in the IRC analysis in the case of a complete response

### ***CNS Efficacy***

Results of ORR and DOR for CNS metastases in a subgroup of 50 patients (pooled from both Studies 1 and 2) who had measurable CNS lesions at baseline according to RECIST v1.1 are summarised in Table 3. Thirty-four (68%) patients with measurable CNS lesions had received prior brain radiation, including 25 (50%) who had completed radiation treatment at least 6 months before starting treatment with ALECENSA. Responses were observed irrespective of prior brain radiation status.

**Table 3. Efficacy results in the patients in Studies 1 and 2 combined who had measurable CNS lesions at baseline**

Efficacy Parameter	n=50
<b>CNS ORR*</b> (95% CI)	64.0% (49.2; 77.1)
<b>Complete Response (CR)</b>	22%
<b>Partial Response (PR)</b>	42%
<b>CNS DOR in months</b> (95% CI)	11.1 (7.6; NE)

\* Proportion of patients with CR or PR of baseline CNS lesions based on radiographic review by IRC

CI=confidence interval; ORR=objective response rate; DOR=duration of response; NE=not estimable

### ***Quality of life (QoL)***

In Study 1, 79 patients (91%) completed questionnaires at baseline and during treatment to assess QoL. The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and Lung Cancer subscale (LC13) were used, in which clinically meaningful improvement is defined as a change from baseline of  $\geq 10$  points. A median change of 16.7 points was seen in the 'Global Health Status' domain (during Weeks 6 to 30). There were no detriments meeting the threshold for clinically meaningful change in any of the subscales assessed.

## **INDICATIONS**

ALECENSA is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.

## **CONTRAINDICATIONS**

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

## **PRECAUTIONS**

### ***Interstitial lung disease (ILD)/pneumonitis***

Cases of severe ILD/pneumonitis have been reported with ALECENSA in clinical trials and post-marketing, including severe ILD/pneumonitis (Grade 3) in one patient (0.4%) out of 253 patients exposed in the Phase I/II clinical trials (Studies 1 and 2). Promptly investigate worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough and fever) in any patient taking ALECENSA. Immediately withhold treatment with ALECENSA in patients diagnosed with ILD/pneumonitis and permanently discontinue it if no other potential causes of ILD/pneumonitis are identified (see DOSAGE AND ADMINISTRATION).

### ***Hepatotoxicity***

In the Phase I/II clinical trials (Studies 1 and 2), elevations of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin (including cases of blood bilirubin increased, hyperbilirubinaemia and bilirubin conjugated increased) were commonly reported as adverse events (incidences of 14%, 16% and 17% respectively). These were generally low grade, transient rises that occurred within the first three months of treatment and resolved with temporary interruption of ALECENSA treatment or dose reduction. Treatment interruption for ALT, AST or bilirubin rise occurred in 3.2%, 1.2% and 5.1% of patients, respectively. Dose reduction for ALT, AST or bilirubin rise occurred in 0.8%, 1.6% and 2.8% of patients, respectively.

In the same studies, higher grade elevations of ALT and AST (greater than 5-fold the ULN) occurred in 3.2% and 2.8% of patients, respectively. Two of these patients (0.8%) had documented drug-induced liver injury (DILI) on liver biopsy. Elevations of bilirubin greater than 3-fold the ULN occurred in 3.2% of patients. In 1.6%, 1.2% and 1.6% of patients, ALT, AST and bilirubin elevations, respectively, led to withdrawal from treatment with ALECENSA. 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 (0.2%) treated in alectinib clinical trials.

Test for liver function (including ALT, AST, and total bilirubin) at baseline and then every 2 weeks during the first 3 months of treatment. Test periodically during treatment thereafter, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the reaction, withhold ALECENSA and resume at a reduced dose, or permanently discontinue ALECENSA as described under DOSAGE AND ADMINISTRATION.

### ***Bradycardia***

There were 14 cases of sinus bradycardia (5.5%) and 7 cases of bradycardia (2.8%) reported in the Phase I/II clinical trials, some of which were symptomatic. None were severe or serious. Of 221 patients treated with ALECENSA who had serial ECGs available 20% had post-dose heart rates slower than 50 beats per minute (bpm).

Heart rate and blood pressure should be monitored regularly. No dose modification is required for asymptomatic bradycardia. If symptomatic or life-threatening bradycardia occurs, adjust ALECENSA treatment as described under DOSAGE AND ADMINISTRATION.

### ***Severe myalgia and creatinine phosphokinase (CPK) elevation***

Adverse events of myalgia/musculoskeletal pain were reported very commonly (30.8%) in patients treated with ALECENSA in the Phase I/II clinical trials. The majority of events were Grades 1 or 2 and three patients (1.2%) had a Grade 3 event. The ALECENSA dose was modified for two patients (0.8%), due to these events. Elevations of CPK occurred in 46% of 219 patients who had their CPK measured, and ten of these patients (5.0%) had Grade 3 elevations. Dose modifications for elevation of CPK occurred in 5.0% of patients.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every fortnight 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 DOSAGE AND ADMINISTRATION).

### ***Photosensitivity***

Photosensitivity and/or sunburn occurred in 30 (11.9%) patients exposed to ALECENSA in the Phase I/II clinical trials. Study participants were advised to avoid sun exposure and to use broad-spectrum sunscreen. All events were Grade 1 severity except for one Grade 2 event.

Advise patients that they should avoid prolonged sun exposure and use a broad-spectrum Ultraviolet A (UVA)/Ultraviolet B (UVB) sunscreen and lip balm (both SPF  $\geq$ 50) whilst taking ALECENSA and for at least 7 days after discontinuation.

### ***Effects on fertility***

No fertility-specific studies of alectinib in animals have been performed.

### ***Use in pregnancy – Category D***

In animal studies, a maternal dose of alectinib (27 mg/kg/day) equivalent to 2.7-times the recommended human dose of 600 mg twice-daily (based on AUC) caused embryo-fetal loss (miscarriage), visceral malformation (retro-oesophageal subclavian) and skeletal variations (an increase in full supernumerary ribs and a corresponding decrease in short supernumerary ribs) in pregnant rabbits. The same dose given to pregnant rats (4 times the clinical AUC) resulted in total litter loss. Alectinib at 9 mg/kg/day (2.5 times the clinical AUC) caused small fetuses and fetal abnormalities (dilated ureter, thymic cord, small ventricle and thin ventricle wall of the heart, and decreased number of sacral and caudal vertebrae).

Based on animal studies and its mechanism of action, ALECENSA may cause fetal harm if taken during pregnancy. No clinical studies of ALECENSA in pregnant women have been performed.

Advise a pregnant woman of the potential harm to the fetus.

Advise females of reproductive potential to avoid pregnancy by using highly effective contraception during treatment with ALECENSA and for at least 1 week after the final dose.

Based on genotoxicity findings (see PRECAUTIONS – Genotoxicity), advise males with female partners of reproductive potential to use highly effective contraception during treatment with ALECENSA and for 3 months following the final dose.

Advise patients that they must inform their healthcare provider of a known or suspected pregnancy.

The use of ALECENSA during labor and delivery has not been established.

### ***Use in lactation***

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breastfed infant, or its effects on milk production. Because of the potential for serious adverse reactions from alectinib in breastfed infants, advise a lactating woman not to breast-feed during treatment with ALECENSA and for 1 week after the final dose.

### ***Paediatric use***

The safety and efficacy of ALECENSA in children and adolescents below 18 years of age have not been established.

Animal Data: Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with doses of  $\geq 27$  mg/kg/day ( $AUC_{0-24h}$  38200 ng.h/mL) alectinib resulted in changes in the growing teeth and bones. Findings in teeth included discoloration and changes in tooth size along with histopathological disarrangement of the ameloblast and odontoblast layers and degeneration/necrosis of ameloblasts. There were also decreases in the trabecular bone and increased osteoclast activity in the femur and sternum. Increased plasma alkaline phosphatase (ALP) of the bone isoform was observed at alectinib doses  $\geq 6$  mg/kg/day ( $AUC_{0-24h}$  13900 ng.h/mL).

### ***Use in the elderly***

Age does not have an effect on ALECENSA exposure (see PHARMACOLOGY, Pharmacokinetics in Special Populations). However, clinical studies of ALECENSA did not include sufficient number of subjects aged 65 and older to determine whether they respond differently from younger subjects.

### ***Genotoxicity***

Alectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay but induced a slight increase in numerical aberrations in the in vitro cytogenetic assay using Chinese Hamster Lung (CHL) cells with metabolic activation, and micronuclei in a rat bone marrow micronucleus test. The mechanism of micronucleus induction was abnormal chromosome segregation (aneugenicity), and not a clastogenic effect on chromosomes.

### ***Carcinogenicity***

Carcinogenicity studies have not been performed to establish the carcinogenic potential of ALECENSA.

### ***Ability to Drive and Use Machines***

No studies of the effects on the ability to drive and to use machines have been performed.



Caution should be exercised when driving or operating machines as patients may experience symptomatic bradycardia (e.g. syncope, dizziness, hypotension) or vision disorders while taking ALECENSA (see ADVERSE EFFECTS).

## **INTERACTIONS WITH OTHER MEDICINES**

### ***Effects of alectinib on other medicines***

#### *CYP substrates*

*In vitro* studies suggest that alectinib and M4 do not inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6. No clinically meaningful effect on the exposure of midazolam (a sensitive CYP3A substrate) or repaglinide (a sensitive CYP2C8 substrate) is expected following co-administration with ALECENSA. No dose adjustment is required for co-administered CYP3A substrates.

#### *P-gp and BCRP substrates*

*In vitro* studies suggest that alectinib and M4 inhibit P-gp and 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). Appropriate monitoring is recommended when ALECENSA is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate).

#### *Other transporters*

Alectinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transport activity *in vitro*.

### ***Effects of other medicines on alectinib***

#### *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.

#### *Medicinal products 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.

## **ADVERSE EFFECTS**

### ***Clinical trials***

The safety of ALECENSA has been evaluated in two Phase I/II clinical trials (Studies 1 and 2) in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with the recommended dose of 600 mg twice daily. Due to the single-arm design of these trials, no control adverse event data is available, and treatment emergent adverse event data is presented below. The median duration of exposure to ALECENSA was 11 months (range 0-35 months) with 169 patients (67%) exposed for more than 6 months, and 123 patients (49%) for more than 12 months. The characteristics of the population were: median age 53 years, 86% aged less than 65 years, 55% female, 74% White/18% Asian, 96% NSCLC adenocarcinoma histology, 98% never or former smokers, 91% with ECOG performance status 0 or 1, and 78% had prior chemotherapy treatment.

The most common adverse events ( $\geq 20\%$ ) were fatigue (44%, includes fatigue and asthenia), constipation (36%), oedema (34%, includes peripheral, generalised, eyelid, periorbital), myalgia (31%, includes myalgia and musculoskeletal pain), nausea (22%), cough (21%), rash (20%, includes rash, maculopapular rash, acneiform dermatitis, erythema, generalised rash, papular rash, pruritic rash, and macular rash) and headache (20%).

The following adverse events of specific concern are discussed in detail in the PRECAUTIONS section:

- Interstitial Lung Disease (ILD)/pneumonitis
- Hepatotoxicity
- Bradycardia
- Severe myalgia and creatine phosphokinase (CPK) elevation
- Photosensitivity

Serious adverse events occurred in 22% of patients. The most frequent reported serious adverse events were pulmonary embolism (1.2%), dyspnoea (1.2%) and hyperbilirubinaemia (1.2%). Fatal adverse reactions occurred in 2.8% of patients and included haemorrhage (0.8%), intestinal perforation (0.4%), dyspnoea (0.4%), pulmonary embolism (0.4%), endocarditis (0.4%) and unknown adverse reaction (0.4%).

Adverse events led to permanent discontinuation of ALECENSA in 6% of patients, most frequently due to hyperbilirubinaemia (1.6%), increased ALT levels (1.6%), and increased AST levels (1.2%). At least one dose reduction or interruption was required for 33% of patients initiating treatment at the recommended dose, and the median time to first dose reduction or interruption was 56 days. The most frequent adverse reactions that led to dose changes were elevations in bilirubin (6.3%), CPK (4.3%), ALT (4.0%) or AST (2.8%), and vomiting (3.2%).

Table 4 summarises the most common treatment-emergent adverse events ( $\geq 10\%$  any grade and  $\geq 2\%$  Grade 3-5) occurring in patients who received ALECENSA in Studies 1 and 2.

**Table 4. Treatment-emergent adverse events occurring very commonly ( $\geq 10\%$ ) at any grade or  $\geq 2\%$  at Grade 3-5 in patients treated with ALECENSA in Studies 1 and 2.**

Adverse Events (MedDRA)	ALECENSA (n=253)	
	All Grades (%)	Grade 3-5* (%)
Fatigue <sup>a</sup>	44	1.6
Constipation	36	0
Oedema <sup>b</sup>	34	0.8
Myalgia <sup>c</sup>	31	1.2
Nausea	22	0.4
Cough	21	0
Rash <sup>d</sup>	20	0.4
Headache	20	1.2
Diarrhoea	18	1.2
Dyspnoea	17	3.6 <sup>e</sup>
Back Pain	15	0
Upper respiratory tract infection	14	0
Vomiting	13	0.4
Increased weight	13	0.8
Vision disorder <sup>f</sup>	12	0
Dizziness	12	0
Photosensitivity reaction <sup>g</sup>	12	0
Insomnia	10	0

\* Per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

<sup>a</sup> Includes fatigue and asthenia

<sup>b</sup> Includes peripheral oedema, oedema, generalised oedema, eyelid oedema, periorbital oedema

<sup>c</sup> Includes myalgia and musculoskeletal pain

<sup>d</sup> Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalised rash, papular rash, pruritic rash and macular rash

<sup>e</sup> Includes one Grade 5 event

<sup>f</sup> Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia

<sup>g</sup> Includes photosensitivity reaction and sunburn

### Laboratory Abnormalities

Table 5 summarises the most common treatment-emergent shifts in key laboratory abnormalities occurring in patients who received ALECENSA in Studies 1 and 2.

**Table 5. Treatment-emergent shifts in key laboratory abnormalities occurring in  $\geq 20\%$  (all Grades) or  $\geq 2\%$  (Grade 3-4) of patients treated with ALECENSA in Studies 1 and 2.**

Parameter	ALECENSA N= 250	
	All Grades (%)	Grade 3 -4* (%)
<b>Chemistry</b>		
Increased AST	53	3.6
Increased ALP	50	1.2
Increased CPK <sup>a</sup>	46	5.0
Hyperbilirubinaemia	42	3.2
Hyperglycaemia <sup>b</sup>	40	2.0
Increased ALT	36	4.8
Hypocalcaemia	35	0.4
Hypokalaemia	31	4.4
Increased creatinine <sup>c</sup>	31	0
Hypophosphataemia	23	3.2
Hyponatraemia	25	2.0
<b>Haematology</b>		
Anaemia	60	2.0
Lymphopenia <sup>d</sup>	25	4.6

AST=aspartate aminotransferase; ALP=alkaline phosphatase; CPK=creatine phosphokinase; ALT=alanine aminotransferase

\* Per CTCAE version 4.0

<sup>a</sup> n=219 for CPK (baseline values missing for 92 patients, presumed normal in generating statistics)

<sup>b</sup> n=152 for fasting blood glucose (baseline values missing for 5 patients)

<sup>c</sup> According to CTCAE criteria based on ULN, and not baseline values

<sup>d</sup> n=218 for lymphocyte count (with baseline values missing for 6 of these patients)

## DOSAGE AND ADMINISTRATION

### *Standard Dosage*

The recommended dose of ALECENSA is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg).

ALECENSA hard capsules should be swallowed whole and must not be opened or dissolved.

### *Duration of Treatment*

Treatment with ALECENSA should be continued until disease progression or unacceptable toxicity.

### *Delayed or Missed Doses*

Advise patients that if a dose of ALECENSA is missed, or if the patient vomits after taking a dose of ALECENSA, patients should be advised not to take an extra dose, but to take the next dose at the regular 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 (Table 6). Dose modification guidelines for specific adverse events are provided in Table 7 (see also PRECAUTIONS). ALECENSA treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

**Table 6. ALECENSA general dose reduction schedule**

Dose event	Change dose to
Starting Dose	600 mg twice daily
First dose reduction	450 mg twice daily
Second dose reduction	300 mg twice daily

**Table 7. Dose modification guidelines for specific adverse events (see also PRECAUTIONS)**

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.

**Attachment 1: Product information for AusPAR Alecensa Alectinic hydrochloride Roche Products Pty Limited PM-2015-04677-1-4 Final 27 November 2017. This Product Information was approved at the time this AusPAR was published.**

Grade	ALECENSA Treatment
ALT or AST elevation of Grade $\geq 3$ ( $> 5$ times ULN) with total bilirubin $\leq 2$ times ULN	Temporarily withhold until recovery to baseline or $\leq$ Grade 1 ( $\leq 3$ times ULN), then resume at reduced dose (see Table 6).
ALT or AST elevation of Grade $\geq 2$ ( $> 3$ times ULN) with total bilirubin elevation $> 2$ times ULN in the absence of cholestasis or haemolysis	Permanently discontinue ALECENSA.
Bradycardia <sup>a</sup> Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	<p>Temporarily withhold until recovery to <math>\leq</math> Grade 1 (asymptomatic) bradycardia or to a heart rate of <math>\geq 60</math> bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications.</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to <math>\leq</math> Grade 1 (asymptomatic) bradycardia or to a heart rate of <math>\geq 60</math> bpm.</p> <p>If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose (see Table 6) upon recovery to <math>\leq</math> Grade 1 (asymptomatic) bradycardia or to a heart rate of <math>\geq 60</math> bpm.</p>
Bradycardia <sup>a</sup> Grade 4 (life-threatening consequences, urgent intervention indicated)	<p>Permanently discontinue if no contributing concomitant medication is identified.</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 6) upon recovery to <math>\leq</math> Grade 1 (asymptomatic) bradycardia or to a heart rate of <math>\geq 60</math> bpm, with frequent monitoring as clinically indicated.</p> <p>Permanently discontinue in case of recurrence.</p>
CPK elevation $> 5$ times ULN	Temporarily withhold until recovery to baseline or to $\leq 2.5$ times ULN, then resume at same dose.

<b>Grade</b>	<b>ALECENSA Treatment</b>
CPK elevation > 10 times ULN or second occurrence of CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to $\leq 2.5$ times ULN, then resume at reduced dose as per Table 6.

ILD=interstitial lung disease; ALT = alanine transaminase; AST =aspartate transaminase; ULN=upper limit of normal; CPK=creatinine phosphokinase

<sup>a</sup> Bradycardia=heart rate less than 60 beats per minute (bpm)

### ***Special Dosage Instructions***

#### *Children*

The safety and efficacy of ALECENSA in children and adolescents below 18 years of age have not been established.

#### *Elderly*

No dose adjustment of ALECENSA is required in patients  $\geq 65$  years of age.

#### *Renal Impairment*

No dose adjustment is required in patients with renal impairment (see PHARMACOLOGY, Pharmacokinetics in Special Populations).

#### *Hepatic Impairment*

No dose adjustment is required in patients with mild hepatic impairment. ALECENSA has not been studied in patients with moderate to severe hepatic impairment (see PHARMACOLOGY, Pharmacokinetics in Special Populations).

## **OVERDOSAGE**

No experience with overdosage is available from the pivotal clinical trials and there is no specific antidote for overdosage with ALECENSA. Patients who experience overdose should be closely supervised and supportive care instituted. Alectinib is >99% bound to plasma proteins and haemodialysis is likely to be ineffective in the treatment of overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## **PRESENTATION AND STORAGE CONDITIONS**

ALECENSA capsules, containing 150 mg alectinib, are white capsules with “ALE” printed in black ink on the cap and “150 mg” printed in black ink on the body.

ALECENSA capsules are packaged in aluminum foil blister sealed with an aluminum lidding foil containing 8 capsules per blister.

Each ALECENSA multipack contains 224 (4 packs of 56) capsules.

Store below 30°C. Store in the original package to protect from light and moisture.

This medicine should not be used after the expiry date (EXP) shown on the pack.

## **DISPOSAL OF MEDICINES**

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

## **NAME AND ADDRESS OF THE SPONSOR**

Roche Products Pty Limited  
ABN 70 000 132 865  
4- 10 Inman Road  
Dee Why NSW 2099  
AUSTRALIA

Customer enquiries: 1800 233 950

## **POISON SCHEDULE OF THE MEDICINE**

Schedule 4 – Prescription Only Medicine

## **DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)**

14 March 2017