AUSTRALIAN PRODUCT INFORMATION – Alecensa (alectinib)

1. NAME OF THE MEDICINE

Alecensa (alectinib) 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 161.3 mg alectinib hydrochloride equivalent to 150 mg alectinib.

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-5*H*-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.

Excipients with known effect

Each capsule contains 33.7 mg lactose monohydrate and 6 mg sodium (as sodium lauryl sulfate).

For the full list of excipients, see section 6.1 *List of excipients*.

3. PHARMACEUTICAL FORM

White hard capsule of 19.2 mm length 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

Adjuvant treatment of resected non-small cell lung cancer

Alecensa is indicated as adjuvant treatment in adult patients following tumour resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumours ≥4 cm or node positive).

Treatment of metastatic NSCLC

Alecensa is indicated for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC.

4.2 DOSE AND METHOD OF ADMINISTRATION

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.

Dose

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

Duration of Treatment

Adjuvant treatment of resected NSCLC

It is recommended that patients are treated with Alecensa for a total of 2 years, or until disease recurrence or unmanageable toxicity.

Treatment of locally advanced or metastatic NSCLC

It is recommended that patients are treated with Alecensa until disease progression or unmanageable 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 1). Dose modification guidelines for specific adverse events are provided in Table 2 (see also section 4.4 *Special Warnings and Precautions for Use*). Alecensa treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose.

Table 1. Alecensa general dose reduction schedule

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

Table 2. Dose modification guidelines for specific adverse events (see also section 4.4)

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 > 5 times ULN with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ 3 times ULN, then resume at reduced dose (see Table 1).
ALT or AST elevation of > 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.

Grade	Alecensa Treatment
CPK elevation > 10 times ULN or second occurrence of CPK elevation > 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 < 100 g/L (Grade ≥ 2)	Temporarily withhold until resolution, resume at reduced dose (see Table 1) or permanently discontinue.

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

[a] Bradycardia=heart rate less than 60 beats per minute (bpm)

Special populations

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

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

Renal Impairment
No dose adjustment is required in patients with renal impairment (see section 4.4 *Special Warnings and Precautions for Use*).

Hepatic Impairment
No starting dose adjustment is required in patients with underlying mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg given orally twice daily (total daily dose of 900 mg). For all patients with hepatic impairment, appropriate monitoring (e.g. markers of liver function) is advised (see section 4.4 *Special Warnings and Precautions for Use*).

Method of Administration

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

4.3 CONTRAINDICATIONS

Alecensa is contraindicated in patients with a known hypersensitivity to alectinib or any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastrointestinal perforation

Cases of gastrointestinal perforation have been reported in patients at increased risk (e.g. history of diverticulitis, metastases to the gastrointestinal tract, concomitant use of medicinal product with a recognised risk of gastrointestinal perforation) and Alecensa should be used with caution.

Patients should be informed of the signs and symptoms of gastrointestinal perforations and advised to seek rapid medical attention in case of occurrence. Discontinuation of Alecensa in patients who develop gastrointestinal perforation should be considered.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis occurred in 1.3% of patients treated with Alecensa in Studies NP28761, NP28673, ALEX and ALINA. In 0.4% of patients, these events were severe (Grade 3). No Grade 4 or 5 events were reported. Five patients (0.9%) in the pooled safety population discontinued Alecensa due to ILD/pneumonitis. Cases of ILD/pneumonitis have also been reported in the post-market setting (see section 4.8 *Adverse Effects (Undesirable effects) - post-marketing*).

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 section 4.2 *Dose and Method of Administration*).

Hepatotoxicity

Elevations in ALT and AST greater than 5-fold the upper limit of normal (ULN) and bilirubin elevations of more than 3 times the ULN were reported in patients in clinical trials with Alecensa. Grade ≥3 elevations of ALT and AST and bilirubin occurred in 3.2%, 3.0 % and 3.4% of patients, respectively, receiving Alecensa in Studies NP28761, NP28673, ALEX and ALINA.

The majority (71% of the patients with hepatic transaminase elevations and 67% of the patients with bilirubin elevations) of these events occurred during the first 3 months of treatment. Discontinuation of Alecensa treatment due to ALT, AST and bilirubin elevations occurred in 1.3%, 1.1% and 1.5% of patients, respectively.

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 (Grade 4 hepatotoxicity) occurred in less than 1% of patients treated in Alecensa clinical trials. Three patients with Grade 3-4 ALT/AST elevations had drug-induced liver injury.

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 section 4.2.

Bradycardia

Symptomatic bradycardia can occur with Alecensa. Cases of bradycardia (11.1%) have been reported in patients treated with Alecensa in Studies NP28761, NP28673, ALEX and ALINA. Of the 521 patients treated with Alecensa who had serial electrocardiograms (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 section 4.2.

Severe myalgia and creatine phosphokinase (CPK) elevation

Myalgia/musculoskeletal pain have been reported very commonly in patients treated with Alecensa in clinical trials. Myalgia events (including musculoskeletal pain and arthralgia) occurred in 34.9% of patients in Studies NP28761, NP28673, ALEX and ALINA. The incidence of Grade 3 myalgia events was 0.9%. Dose modifications for myalgia events were required in 1.7% of patients.

Elevations of CPK occurred in 55.6% of 491 patients with CPK laboratory data available in Studies NP28761, NP28673, ALEX and ALINA. The incidence of Grade ≥ 3 elevations of CPK was 5.5%. Median time to Grade ≥3 CPK elevation was 15 days across clinical trials. Dose modifications for elevation of CPK occurred in 5.3% of patients. In the ALINA study, elevated CPK occurred in 77% of 128 patients with CPK laboratory data, including 6% Grade ≥ 3 elevations.

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 section 4.2 *Dose and Method of Administration*).

Haemolytic anaemia

Haemolytic anaemia was initially reported with Alecensa in the postmarketing setting including cases associated with a negative direct antiglobulin test (DAT) result. Additional assessments for the determination of haemolytic anaemia were subsequently collected in the ALINA study, where it was observed in 3.1% of patients treated with Alecensa (see section 5.1 *Pharmacodynamic properties (clinical trials)* and 4.8 *Adverse Effects (Undesirable Effects*) - *post-marketing)*. If haemoglobin concentration is below 100 g/L 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 *Dose and Method of Administration*).

Photosensitivity

Photosensitivity and/or sunburn occurred in 8.3% of patients exposed to Alecensa in Studies NP28761, NP28673, ALEX and ALINA. Study participants were advised to avoid sun exposure and to use broad-spectrum sunscreen. All events were Grade 1 or 2 severity except for one non-serious Grade 3 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 ≥50) whilst taking Alecensa and for at least 7 days after discontinuation.

Use in 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 metabolite M4. Based on a population pharmacokinetic analysis, alectinib and M4 exposures were similar in patients with mild hepatic impairment and normal hepatic function.

Following administration of a single oral dose of 300 mg alectinib in subjects with severe (Child-Pugh C) hepatic impairment, alectinib C_{max} was the same and AUC_{inf} was 2.2-fold higher compared with the same parameters in matched healthy subjects. M4 C_{max} and AUC_{inf} was 39% and 34% lower respectively, resulting in a combined exposure of alectinib and M4 (AUC_{inf}) 1.8-fold higher in patients with severe hepatic impairment compared with matched healthy subjects.

The hepatic impairment study also included a group with moderate (Child-Pugh B) hepatic impairment, and a modestly higher alectinib exposure was observed in this group compared with matched healthy subjects. The subjects in the Child Pugh B group however did in general not suffer from abnormal bilirubin, albumin or prothrombin time, indicating that they may not be fully representative of moderately hepatically impaired subjects with decreased metabolic capacity.

Use in 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.

Use in the elderly

Nineteen percent of the 533 patients studied in NP28761, NP28673, ALEX and ALINA were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of serious adverse events (38% vs 25%), more frequent adverse events leading to treatment discontinuations (18% vs 6%) and dose modifications (48% vs 35%) in patients 65 years or older as compared to those younger than 65 years.

Paediatric use

The safety and efficacy of Alecensa in children and adolescents below 18 years of age have not been established (see also section 5.3 *Preclinical Safety Data*).

Effects on laboratory tests

No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Contraception in males and females

Alecensa may cause fetal harm when administered to a pregnant woman (see below). Advise females of reproductive potential to avoid pregnancy by using highly effective contraception during treatment with Alecensa and for at least 5 weeks after the final dose.

Based on genotoxicity findings (see section 5.3 *Preclinical Safety Data*), 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.

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

The use of Alecensa during labour 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 breastfeed during treatment with Alecensa and for 1 week after the final dose.

4.7 EFFECTS ON 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 section 4.8 *Adverse Effects (Undesirable Effects*)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following adverse events of specific concern are discussed in detail in section 4.4:

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

The safety profile of Alecensa was generally consistent across the phase III clinical trials and the pivotal phase I/II trials (Studies NP28761 and NP28673); however, relevant differences between studies are described in section 4.4.

Clinical trials

Adjuvant treatment of resected ALK-positive NSCLC

The safety of Alecensa was evaluated in ALINA, a multi-centre, open-label, randomised trial for the adjuvant treatment of patients with resected ALK-positive NSCLC (see section 5.1 *Pharmacodynamic properties (clinical trials)*. At the time of DFS analysis, the median duration of exposure was 23.9 months for Alecensa and 2.1 months for platinum-based chemotherapy.

Serious adverse reactions occurred in 13% of patients treated with Alecensa; the most frequent serious adverse reaction was pneumonitis (0.8%). Adverse reactions that led to treatment discontinuation of Alecensa occurred in 5.5% of patients; the most frequent adverse reaction (≥ 2%) that led to treatment discontinuation was pneumonitis (2.3%).

Dose interruptions occurred in 27% of patients treated with Alecensa; the most frequent adverse reactions (≥ 2%) that led to dose interruptions were increased blood creatine phosphokinase (5.5%), increased blood bilirubin (3.9%), increased ALT (5.5%), increased AST (4.7%) and myalgia (2.3%).

Dose reductions occurred in 26% of patients treated with Alecensa; the most frequent adverse reactions (≥2%) that led to dose reductions were increased blood creatine phosphokinase (6.3%) and increased blood bilirubin (3.9%).

Table 3 and 4 summarise the common adverse reactions and laboratory abnormalities observed in ALINA.

Table 3: Adverse Drug Reactions (≥ 10% for all NCI CTCAE Grades or ≥ 2% for Grades 3-4) in Patients Treated with Alecensa in ALINA

Adverse Reaction	Alecensa N= 128		Chemotherapy N = 120	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hepatobiliary Disorders				
Increased ALT	34	1.6*	9	0
Increased AST	41	0.8*	5.0	0
Increased bilirubin[a]	39	2.3	0.8	0
Gastrointestinal Disorders				
Constipation	42	0.8*	25	0.8
Diarrhoea	13	0.8*	8	0.8
Musculoskeletal				
Myalgia[b]	34	0.8*	3.3	0
Blood and Lymphatic System Disorders				
Anaemia[c]	24	0	26	0.8
Skin and Subcutaneous Tissue Disorders				
Rash[d]	17	1.6*	10	0
General Disorders and Administration Site Conditions				
Oedema[e]	16	0	1.7	0
Renal				
Renal Impairment[f]	16	0.8*	8	0
Investigations				
Increased Weight	13	0.8*	0.8	0
Nervous System Disorders				
Dysgeusia[g]	13	0	3.3	0
Cardiac Disorders				
Bradycardia[h]	12	0	0	0
Metabolism and Nutrition Disorders				
Hyperuricaemia[i]	11	0	1.7	0

Based on NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) v5.0

*All events were Grade 3

[a] Includes cases of increased blood bilirubin, hyperbilirubinemia, increased bilirubin conjugated and increased blood bilirubin unconjugated.

[b] Includes myalgia and arthralgia

[c] Includes anaemia, normochromic normocytic anaemia and cases indicative of haemolytic anaemia.

[d] Includes rash, rash maculo-papular, dermatitis acneiform, rash papular, erythema and rash erythematous.

[e] Includes oedema, peripheral oedema, face oedema, localized oedema, peripheral swelling, face swelling.

[f] Includes increased blood creatinine, creatinine renal clearance decreased, renal impairment, renal failure and glomerular filtration rate decreased.

[g] Includes dysgeusia and taste disorder.
[h] Includes bradycardia and sinus bradycardia.
[i] includes cases of hyperuricemia and increased blood uric acid.

The following additional clinically significant adverse reactions (< 10%) were observed in patients treated with Alecensa in ALINA: nausea (7.8%), vomiting (7.0%), vision disorders (4.7%; includes blurred vision, visual acuity reduced and photopsia), stomatitis (4.7%; includes stomatitis and mouth ulceration), photosensitivity reaction (3.9%) and pneumonitis (2.3%).

Table 4: Treatment-Emergent Worsening in Laboratory Values from Baseline Occurring in ⩾ 20% of Patients in Treated with Alecensa in ALINA

Parameter	Alecensa N= 128		Chemotherapy N=120	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased CPK	77	8	8	1.7
Increased AST	75	0.8*	25	0
Increased bilirubin	68	2.3*	4.2	0
Increased alkaline phosphatase	64	0	14	0
Increased ALT	57	2.3*	28	0
Increased creatinine	41	0	23	0
Increased uric acid	30	0	19	0
Haematology				
Decreased haemoglobin	69	0	67	0.8

Based on NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) v5.0
*All events were Grade 3

Patients not previously treated systemically for advanced or metastatic NSCLC

The safety of Alecensa 600 mg twice daily compared to crizotinib 250 mg twice daily was evaluated in 152 and 151 patients with ALK-positive NSCLC, respectively, in the Phase III clinical trial, ALEX. The median duration of exposure to Alecensa and crizotinib was 17.9 and 10.7 months, respectively. Patients presenting with baseline symptomatic bradycardia were not studied in this trial.

Serious adverse reactions occurred in 28% and 29% of patients treated with Alecensa and crizotinib, respectively. The most frequently reported serious adverse reactions were pneumonia (3.3%) and acute kidney injury (2.6%) for patients treated with Alecensa, and pneumonia, pneumonitis and elevated ALT (2.6% each) for patients treated with crizotinib. Grade ≥ 3 adverse events were reported for 41% of patients in the Alecensa arm and 50% in the crizotinib arm. Fatal adverse events occurred in both treatment arms: 5 (3.3%), all unrelated in the Alecensa arm, and 7 (4.6%), 2 related in the crizotinib arm.

Permanent treatment discontinuation for adverse reactions occurred in 11% of patients treated with Alecensa, and in 13% of crizotinib-treated patients. Acute kidney injury was the most commonly reported adverse drug reaction leading to study drug discontinuation in the Alecensa arm (2.0%) and elevated ALT (5.3%), AST (4.0%) and pneumonitis (2.6%) in the crizotinib arm. Dose modifications (dose reductions and drug interruption, respectively) were required in 16% and 19% of patients in the Alecensa arm and in 21% and 25% in the crizotinib arm, respectively. The most frequent adverse reactions that led to dose modifications in the Alecensa arm were pneumonia, elevation in ALT and AST and in the crizotinib arm were elevated ALT, AST, neutropenia and vomiting.

Table 5: Adverse Drug Reactions in > 10% for all NCI CTCAE Grades or ≥ 2% for Grades 3-4 of patients in either treatment arm in ALEX

	Alecensa N = 152		**Crizotinib N= 151**	
MedDRA System Organ Class Adverse Reaction	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Gastrointestinal disorders				
Constipation	34	0	33	0
Nausea	14	0.7	48	3.3
Diarrhoea	12	0	45	2.0
Vomiting	7.2	0	38	3.3
General disorders and administration site conditions				
Oedema[a]	22	0.7	34	0.7
Musculoskeletal and connective tissue disorders				
Myalgia[b]	23	0	4.0	0
Skin and subcutaneous tissue disorders				
Rash[c]	15	0.7	13	0
Nervous system disorders				
Dysgeusia[d]	3.3	0.7	19	0
Eye disorders				
Vision disorders[e]	4.6	0	23	0
Cardiac disorders				
Bradycardia[f]	11	0	15	0
Renal and urinary disorders				
Acute kidney injury	2.6	2.6*	0	0

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities.

[a] Includes cases of peripheral oedema, oedema, eyelid oedema, localised oedema, and face oedema.

[b] Includes cases of myalgia and musculoskeletal pain.

[c] Includes cases of rash, rash maculo-papular, dermatitis acneiform, erythema, generalised rash, rash macular, rash papular, exfoliative rash, and pruritic rash.

[d] Includes cases of dysgeusia and hypogeusia.

[e] Includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, and diplopia.

[f] Includes cases of bradycardia and sinus bradycardia.

* Includes one Grade 5 event.

Additional adverse drug reactions in patients treated with Alecensa compared to crizotinib respectively include weight increased (9.9% vs 0%), photosensitivity reaction (5.3% vs 0%), stomatitis (3.3% vs 2.6%, which includes cases of stomatitis and mouth ulceration), interstitial lung disease (1.3% vs. 6.0%, which includes cases of interstitial lung disease and pneumonitis), and hepatotoxicity (1.4% vs. 0.7%, which includes cases of drug-induced liver injury, 0.7% vs 0.7, and hepatotoxicity).

Table 6 summarises treatment-emergent shifts in laboratory abnormalities with Alecensa in ALEX.

Table 6: Treatment-emergent shifts in laboratory abnormalities that occurred in > 10% in Alecensa-treated patients in ALEX

Parameter	**Alecensa N= 152**		**Crizotinib N=151**	
	All Grades (%)	**Grade 3–4[a] (%)**	**All Grades (%)**	**Grade 3–4[a] (%)**
Chemistry				
Increased blood bilirubin	53[c]	5.5[c]	4.7[g]	0
Increased AST	50[d]	6.2[d]	56[g]	11[g]
Increased ALP	50[e]	0	44[g]	0
Increased ALT	40[e]	6.1[e]	62[g]	16[g]
Increased blood creatinine[b]	38[e]	3.4[e]	23[g]	0.7[g]
Increased CPK	37 [f]	3.1[f]	51[h]	1.5[h]
Haematology				
Decreased haemoglobin	62[e]	6.8[e]	36[g]	0.7[g]

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

Note: Laboratory abnormalities were based on the normal ranges of the National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] No Grade 5 laboratory abnormalities were reported.

[b] Only patients with creatinine increases based on ULN definition.

Patients with missing baseline and/or no post-baseline lab assessments were excluded from analyses: c; N=146, d; N=145, e; N=147, f; N=129, g; N=148, h; N=130

Crizotinib pre-treated patients

The safety of Alecensa has been evaluated in two Phase I/II clinical trials (Studies NP28761 and NP28673) 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 (≥ 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%).

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 7 summarises the most common treatment-emergent adverse events (≥10% any grade and ≥2% Grade 3-5) occurring in patients who received Alecensa (600 mg twice daily) in Studies NP28761 and NP28673.

Table 7. Treatment-emergent adverse events occurring very commonly (≥10%) at any grade or ≥2% at Grade 3-5 in patients treated with Alecensa in Studies NP28761 and NP28673.

Adverse Events (MedDRA)	**Alecensa 600 mg twice daily (n=253)**	
System Organ Class	**All Grades (%)**	**Grade 3–5[*] (%)**
Fatigue[a]	44	1.6
Constipation	36	0
Oedema[b]	34	0.8
Myalgia[c]	31	1.2
Nausea	22	0.4
Cough	21	0
Rash[d]	20	0.4
Headache	20	1.2
Diarrhoea	18	1.2
Dyspnoea	17	3.6[e]
Back Pain	15	0

Adverse Events (MedDRA)	Alecensa 600 mg twice daily (n=253)	
Upper respiratory tract infection	14	0
Vomiting	13	0.4
Increased weight	13	0.8
Vision disorder[f]	12	0
Dizziness	12	0
Photosensitivity reaction[g]	12	0
Insomnia	10	0

* Per Common Terminology Criteria for Adverse Events (CTCAE) v4.0

[a] Includes fatigue and asthenia

[b] Includes peripheral oedema, oedema, generalised oedema, eyelid oedema, periorbital oedema

[c] Includes myalgia and musculoskeletal pain

[d] Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalised rash, papular rash, pruritic rash and macular rash

[e] Includes one Grade 5 event

[f] Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia

[g] Includes photosensitivity reaction and sunburn

Table 8 summarises the most common treatment-emergent shifts in key laboratory abnormalities occurring in patients who received Alecensa in Studies NP28761 and NP28673.

Table 8. Treatment-emergent shifts in key laboratory abnormalities occurring in ≥ 20% (all Grades) or ≥ 2% (Grade 3-4) of patients treated with Alecensa in Studies NP28761 and NP28673.

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

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

[*] Per CTCAE version 4.0
[a] n=219 for CPK (baseline values missing for 92 patients, presumed normal in generating statistics)
[b] n=152 for fasting blood glucose (baseline values missing for 5 patients)
[c] According to CTCAE criteria based on ULN, and not baseline values
[d] n=218 for lymphocyte count (with baseline values missing for 6 of these patients)

Post-Marketing

The adverse drug reactions of increased alkaline phosphatase, haemolytic anaemia and hyperuricaemia were reported with Alecensa in the post-marketing setting as well as during clinical trials (see section 5.1 *Pharmacodynamic properties (clinical trials)*).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC code: L01ED03

Mechanism of Action

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

In nonclinical 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.

Clinical trials

Adjuvant treatment of resected ALK-Positive non-small cell lung cancer

The efficacy of Alecensa for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumour resection was established in a global randomised Phase III open-label clinical trial ALINA (BO40336). Eligible patients were required to have Stage IB (tumours ⩾ 4 cm) – IIIA NSCLC per the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) Staging System, 7th Edition, with ALK-positive disease identified by a locally performed FDA-approved or CE-marked ALK test, or centrally performed by the Ventana ALK (D5F3) immunohistochemistry (IHC) assay.

Patients were randomised (1:1) to receive Alecensa 600 mg orally twice daily or platinum-based chemotherapy following tumour resection. Randomization was stratified by race (Asian and non-Asian) and stage of disease. Alecensa was administered at the recommended oral dose of 600 mg twice daily for a total of 2 years, or until disease recurrence or unmanageable toxicity. Platinum-based chemotherapy was administered intravenously for 4 cycles, with each cycle lasting 21 days, according to one of the following regimens:

- Cisplatin 75 mg/m^2 on Day 1 plus vinorelbine 25 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus gemcitabine 1250 mg/m^2 on Days 1 and 8
- Cisplatin 75 mg/m^2 on Day 1 plus pemetrexed 500 mg/m^2 on Day 1

In the event of intolerance to a cisplatin-based regimen, carboplatin was administered instead of cisplatin in the above combinations at a dose of area under the free carboplatin plasma concentration versus time curve (AUC) 5 mg/mL/min or 6 mg/mL/min.

The major efficacy outcome measures were disease-free survival (DFS) in patients with stage II-IIIA NSCLC and DFS in patients with stage IB-IIIA (intent to treat, ITT) as assessed by investigator. . DFS was defined as the time from the date of randomisation to the date of occurrence of any of the following: first documented recurrence of disease, new primary NSCLC, or death due to any cause, whichever occurred first. The secondary and exploratory efficacy endpoints were overall survival (OS) and time to CNS recurrence or death (CNS-DFS).

A total of 257 patients were studied; 130 patients were randomised to the Alecensa arm, and 127 patients were randomised to the chemotherapy arm. Overall, the median age was 56 years (range: 26 to 87), 24% were ⩾ 65 years old, 52% were female, 56% were Asian, 60% were never smokers, 53% had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 10% of patients had Stage IB, 36% had Stage II and 54% had Stage IIIA disease.

ALINA demonstrated a statistically significant and clinically meaningful improvement in DFS for patients treated with Alecensa compared to patients treated with chemotherapy in the Stage II-IIIA and the Stage IB-IIIA (ITT) patient populations. OS data were not mature at the time of

DFS analysis with 2.3% of deaths reported overall. The median duration of survival follow-up was 27.8 months in the Alecensa arm and 28.4 months in the chemotherapy arm.

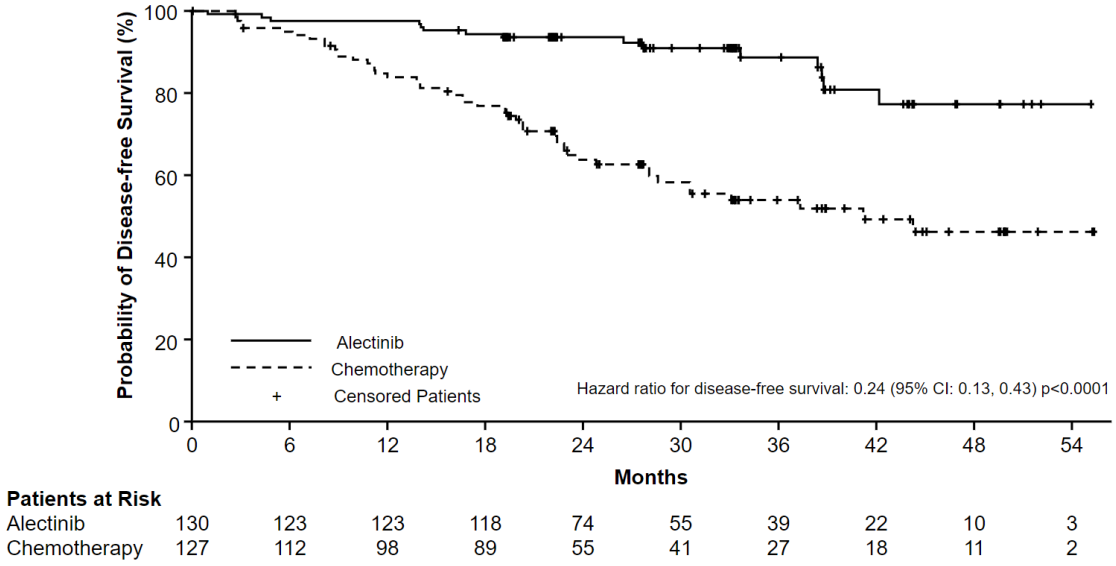
The DFS efficacy results are summarized in Table 9, and Figure 1.

Table 9: Investigator Assessed DFS Results in ALINA

Efficacy Parameter	Stage II-IIIA Population		ITT Population	
	Alecensa N=116	Chemotherapy N=115	Alecensa N=130	Chemotherapy N=127
Number of DFS Events (%)	14 (12.1)	45 (39.1)	15 (11.5)	50 (39.4)
Median DFS, months (95% CI)	NE (NE, NE)	44.4 (27.8, NE)	NE (NE, NE)	41.3 (28.5, NE)
Stratified HR (95% CI)*	0.24 (0.13, 0.45)		0.24 (0.13, 0.43)	
p-value (log-rank)*	<0.0001		<0.0001	

DFS = Disease-Free Survival; ITT = Intent-to-Treat; CI = Confidence Interval; NE = Not Estimable; HR = Hazard Ratio *Stratified by race in Stage II-IIIA, stratified by race and stage in Stage IB-IIIA.

Figure 1: Kaplan-Meier Curve of Disease-Free Survival in the ITT Population



An exploratory analysis of the site(s) of relapse showed the proportion of patients with brain involvement at the time of disease recurrence was 4 patients (3.1%) in the Alecensa arm and 14 patients (11.0%) in the chemotherapy arm in the ITT population.

Patients not previously treated systemically for advanced or metastatic NSCLC

The safety and efficacy of Alecensa were studied in a global randomised Phase III open label clinical trial (ALEX) in ALK-positive NSCLC patients not previously treated systemically for advanced or metastatic NSCLC. Central testing for ALK protein expression positivity of tissue samples from all patients by Ventana anti-ALK (D5F3) immunohistochemistry (IHC)

was required before randomisation into the study. Retrospective ALK testing using the Vysis fluorescence *in situ* hybridisation (FISH) assay was also performed.

A total of 303 patients were included in the Phase III trial, 151 patients randomised to the crizotinib arm and 152 patients randomised to the Alecensa arm receiving Alecensa orally, at the recommended dose of 600 mg twice daily.

ECOG performance status (0/1 vs. 2), race (Asian vs. non-Asian), and CNS metastases at baseline (yes vs. no) were stratification factors for randomisation. The primary endpoint of the trial was to demonstrate superiority of Alecensa versus crizotinib based on Progression Free Survival (PFS) as per investigator assessment using RECIST 1.1. Baseline demographic and disease characteristics for Alecensa were median age 58 years (54 years for crizotinib) , 55% female (58% for crizotinib), 55% non-Asian (54% for crizotinib), 61% with no smoking history (65% for crizotinib), 93% ECOG performance status of 0 or 1 (93% for crizotinib), 97% Stage IV disease (96% for crizotinib), 90% adenocarcinoma histology (94% for crizotinib), 40% CNS metastases at baseline (38% for crizotinib) and 17% having received prior CNS radiation (14% for crizotinib).

The trial met its primary endpoint at the primary analysis. Efficacy data are summarised in Table 10 and the Kaplan-Meier curves for investigator and Independent Review Committee (IRC)-assessed PFS are shown in Figures 2 and 3.

Table 10. Summary of efficacy results in ALEX

	Crizotinib N=151	**Alecensa N=152**
Median duration of follow-up (months)	17.6 (range 0.3 – 27.0)	18.6 (range 0.5 – 29.0)
Primary Efficacy Parameter		
PFS (INV) Number of patients with event n (%) Median (months) [95% CI]	 102 (68%) 11.1 [9.1; 13.1]	 62 (41%) NE [17.7; NE]
HR [95% CI] Stratified log-rank p-value	0.47 [0.34, 0.65] p <0.0001	
Secondary efficacy parameters		
PFS (IRC)* Number of patients with event n (%) Median (months) [95% CI]	 92 (61%) 10.4 [7.7; 14.6]	 63 (41%) 25.7 [19.9; NE]
HR [95% CI] Stratified log-rank p-value	0.50 [0.36; 0.70] p < 0.0001	
Time to CNS progression (IRC)* (without prior systemic PD**) Number of patients with event n (%)	 68 (45%)	 18 (12%)
Cause-Specific HR	0.16	

	Crizotinib N=151	Alecensa N=152
[95% CI] Stratified log-rank p-value	[0.10; 0.28] p < 0.0001	
12-month cumulative incidence of CNS progression (IRC) % (95% CI)	41.4% [33.2; 49.4]	9.4% [5.4; 14.7]
ORR (INV)*, *** Responders n (%) [95% CI]	 114 (75.5%) [67.8; 82.1]	 126 (82.9%) [76.0; 88.5]
Overall survival* Number of patients with event n (%)* Median (months) [95% CI]	 40 (27%) NE [NE; NE]	 35 (23%) NE [NE; NE]
HR [95% CI]	0.76 [0.48; 1.20]	
Duration of response (INV) Median (months) 95 % CI	N=114 11.1 [7.9; 13.0]	N=126 NE [NE; NE]
CNS-ORR in patients with measurable CNS metastases at baseline CNS responders n (%) [95% CI] CNS-CR n (%) CNS-DOR , median (months) 95% CI	N=22 11 (50.0%) [28.2; 71.8] 1 (5%) 5.5 [2.1, 17.3]	N=21 17 (81.0%) [58.1; 94.6] 8 (38%) 17.3 [14.8, NE]
CNS-ORR in patients with measurable and non-measurable CNS metastases at baseline (IRC) CNS responders n (%) [95% CI] CNS-CR n (%) CNS-DOR , median (months) 95% CI	N=58 15 (25.9%) [15.3%; 39.0%] 5 (9%) 3.7 [3.2, 6.8]	N=64 38 (59.4%) [46.4%; 71.5%] 29 (45%) NE [17.3, NE]

Data cutoff date: 9 February 2017

* Key secondary endpoints part of the hierarchical testing

** Competing risk analysis of CNS progression, systemic progression and death as competing events

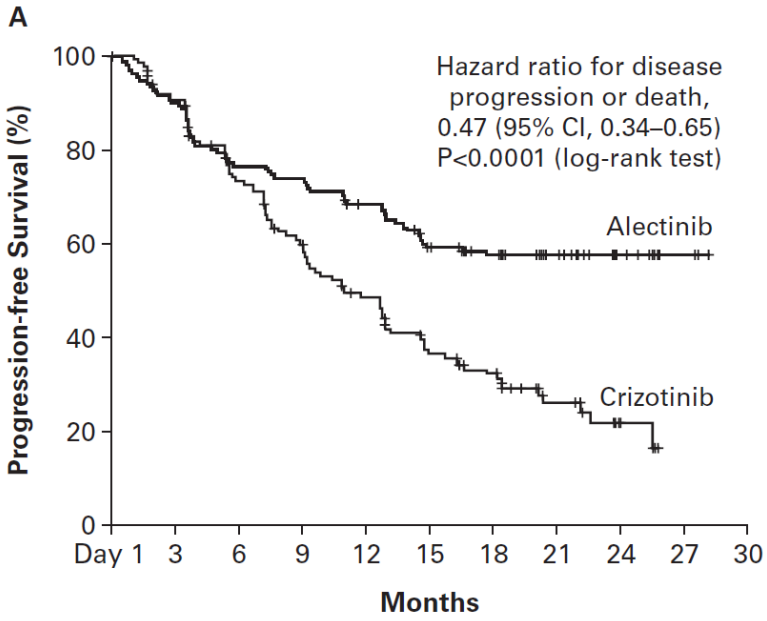
*** 2 patients in the crizotinib arm and 6 patients in the alectinib arm had CR

CI = confidence interval; CNS = central nervous system; CR = complete response; DOR = duration of response; HR = hazard ratio; IRC = Independent Review Committee; INV = investigator; NE = not estimable; ORR = objective response rate; PFS = progression-free survival

The magnitude of PFS benefit was consistent for patients with CNS metastases at baseline (HR=0.40, 95% CI: 0.25-0.64, median PFS for Alecensa = NE, 95% CI: 9.2-NE, median PFS

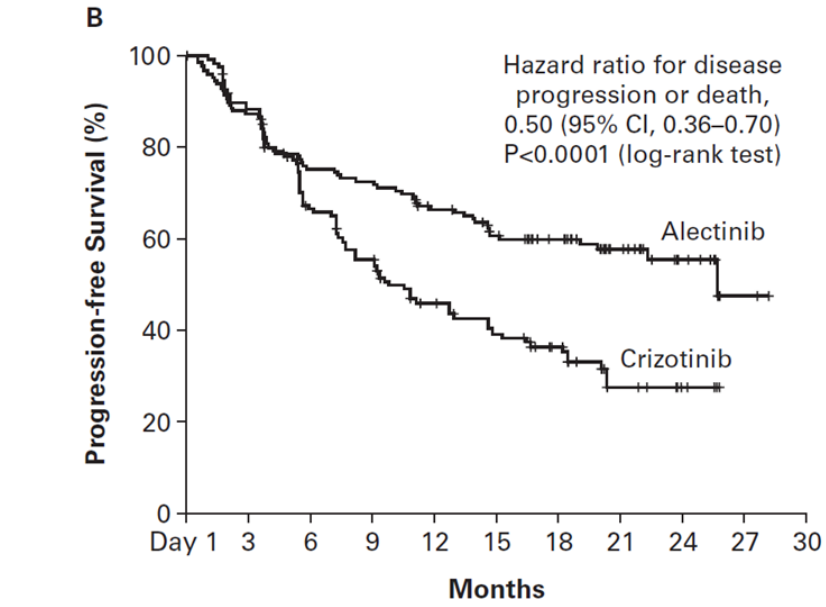
for crizotinib = 7.4 months, 95% CI: 6.6-9.6) and without CNS metastases at baseline (HR = 0.51, 95% CI: 0.33-0.80, median PFS for Alecensa = NE, 95% CI: NE, NE, median PFS for crizotinib = 14.8 months, 95% CI:10.8-20.3), indicating benefit of Alecensa over crizotinib in both subgroups.

Figure 2: Kaplan Meier Plot of INV-Assessed PFS in ALEX



No. at Risk										
Crizotinib	151	132	104	84	65	46	35	16	5	
Alectinib	152	135	113	109	97	81	67	35	15	3

Figure 3: Kaplan Meier Plot of IRC Assessed PFS in ALEX



Crizotinib pre-treated patients

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 clinical trials, Studies, NP28761 and NP28673. 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. NP28673 included as co-primary endpoint evaluation of ORR by IRC using RECIST v1.1 in patients with prior exposure of cytotoxic chemotherapy treatments.

NP28761 was conducted in North America and included 87 patients in the Phase II part of the study. Baseline demographic and disease characteristics in NP28761 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.

NP28673 was conducted internationally and included 138 patients in the Phase II part of the study. Baseline demographic and disease characteristics in NP28673 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 NP28761 and NP28673 in all treated patients are summarised in Table 11. The median duration of follow-up was 17 months in NP28761 and 21 months in NP28673 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 NP28761 and NP28673, respectively.

Table 11. Efficacy results in Studies NP28761 and NP28673 (ITT population)

	NP28761[1]		**NP28673[2]**	
Efficacy Parameter	**IRC***	**Investigator**	**IRC***	**Investigator**
ORR in ITT population (95% CI) Number of responders	n=87 42.5% (32.0; 53.6) 37	n=87 52.9% (41.9; 63.7) 46	n=138 44.9% (36.5; 53.6) 62	n=138 51.4% (42.8; 60.0) 71
ORR in patients pre-treated with chemotherapy (95% CI) Number of responders	n/a	n/a	n=110 39.1% (29.9; 48.9) 43	n=110 50.0% (40.3; 59.7) 55
Median DOR (months) in ITT population (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)

[1] Data cutoff date: 22-Jan-2016 [2] 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 NP28761 and 16 patients in NP28673 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) who had measurable CNS lesions at baseline according to RECIST v1.1 are summarised in Table 12. 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 12. Efficacy results in the patients in Studies NP28761 and NP28673 combined who had measurable CNS lesions at baseline

Efficacy Parameter	**n=50**
CNS ORR* **(95% CI)**	64.0% (49.2; 77.1)

Complete Response (CR)	22%
Partial Response (PR)	42%
CNS DOR in months (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 NP28761, 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 ≥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.

5.2 PHARMACOKINETIC PROPERTIES

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 13.

Table 13. Steady-state PK seen with recommended 600 mg twice daily dosing of alectinib [cited as geometric mean (coefficient of variation %)]

PK parameter	Alectinib	M4
Maximal concentration (C_{max})	665 ng/mL (44.3%)	246 ng/mL (45.4%)
Trough concentration (C_{min})	572 ng/mL (47.8%)	222 ng/mL (46.6%)
Area under the curve from 0-12 hours (AUC_{0-12})	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_{0-inf} 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_{ss}) 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 ^{14}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 ^{14}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 (NP28761and NP28673) was undertaken to characterise the PK of alectinib and M4 in special populations.
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. For hepatic and renal impairment, see section 4.4 *Special Warnings and Precautions for Use*.

5.3 PRECLINICAL SAFETY DATA

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.

Juvenile development

Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with doses of ≥ 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 ≥ 6 mg/kg/day (AUC_{0-24h} 13900 ng.h/mL).

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content
Lactose monohydrate
Hyprolose
Sodium lauryl sulfate
Carmellose calcium
Magnesium stearate.

Capsule shell

Carrageenan
Potassium chloride
Titanium dioxide
Carnauba wax
Maize starch
Hypromellose.

Printing ink

Iron oxide red
Iron oxide yellow
Indigo carmine aluminium lake
Carnauba wax
Shellac
Glyceryl monooleate.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

6.5 NATURE AND CONTENTS OF CONTAINER

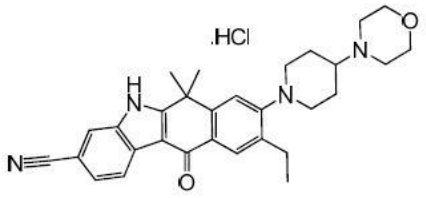
Alecensa capsules are packaged in aluminium foil blister sealed with an aluminium lidding foil containing 8 capsules per blister.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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.

6.7 PHYSICOCHEMICAL PROPERTIES



CAS: 1256589-74-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30-34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

14 March 2017

10. DATE OF REVISION OF THE TEXT

23 December 2024

Summary of Changes Table

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1	Addition of new indication (Adjuvant treatment of ALK-positive NSCLC)
4.6	Increase in contraception duration recommendation for females of child bearing potential