NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Alecensa® (alectinib) 150 mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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.

3 PHARMACEUTICAL FORM

Hard capsule

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

Alecensa is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (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 in first-line.

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).

Patients with underlying severe hepatic impairment should receive a dose of 450 mg (three 150 mg capsules) given orally twice daily with food (total daily dose of 900 mg).

Duration of treatment

It is recommended that patients are treated with Alecensa 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 (see Table 1). Dose modification guidelines for specific adverse events are provided in Table 2 (see also section 4.4). 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 Grade ≥ 3 (> 5 times ULN) with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ Grade 1 (≤ 3 times ULN), then resume at reduced dose (see Table 1).
ALT or AST elevation of Grade ≥ 2 (> 3 times ULN) with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis	Permanently discontinue Alecensa.

Grade	Alecensa Treatment
Bradycardia[a] Grade 2 or 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm.
Bradycardia[a] Grade 4 (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose (see Table 1) upon recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm, with frequent monitoring as clinically indicated. Permanently discontinue in case of recurrence.
CPK elevation > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at same dose.
CPK elevation > 10 times ULN or second occurrence of CPK elevation > 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 (≥ 65 years)

No dose adjustment of Alecensa is required in patients aged 65 years and older.
Age does not have an effect on Alecensa exposure (see section 5.2). 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.

Renal Impairment

No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic Impairment

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

Paediatric population

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

Method of administration

Alecensa is for oral use. The 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

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 (NP28673 and NP28761). In Phase III (BO28984), 2 patients (1.3%) out of 152 patients treated with Alecensa had an ILD event, neither of which was severe (Grade ≥3). There were no fatal cases of ILD in any of the clinical trials.

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).

Hepatotoxicity

In the pivotal clinical trials, 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. In Phase I/II clinical trials (NP28673 and NP28761), the incidences of these events were 14%, 16% and 17%, respectively. In the Phase III clinical trial (BO28984), these events

were reported in 15%, 14% and 21%, respectively. The events 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 in the Phase I/II clinical trials (NP28673 and NP28761) and in 2.6%, 2.0% and 2.6%, respectively, in the Phase III clinical trial (BO28984). In the same studies, dose reduction for ALT, AST or bilirubin rise occurred in 0.8%, 1.6% and 2.8% of patients in studies NP28673 and NP28761 and in 2.0%, 2.6% and 4.6% in study BO28984, respectively.

Higher grade elevations of ALT and AST (greater than 5-fold the ULN) and bilirubin elevations of more than 3 times the ULN were reported. In Phase I/II clinical trials (NP28673 and NP28761), elevations of ALT and AST (greater than 5-fold the ULN) and bilirubin (greater than 3-fold the ULN) occurred in 3.2%, 2.8% and 3.2% of patients, respectively. In the same studies, ALT, AST and bilirubin elevations led to withdrawal from treatment with Alecensa in 1.6%, 1.2% and 1.6% of patients, respectively.

In the Phase III clinical trial (BO28984), elevation of AST greater than 5 times the ULN occurred in 6.2% and elevation of ALT greater than 5 times the ULN occurred in 6.1% of patients treated with Alecensa, respectively. Elevations of bilirubin greater than 3 times the ULN occurred in 5.5% of patients who received Alecensa treatment. The majority (56% of the patients with hepatic transaminase elevations and 69% of the patients with bilirubin elevations) of these events occurred during the first 3 months of treatment. Two patients (1.3%) discontinued Alecensa due to Grade 3–4 adverse events of elevated hepatic transaminases. Alecensa treatment was discontinued due to a Grade 3 adverse event of elevated bilirubin in 1 patient (0.7%).

In the pivotal studies, two patients with Grade 3–4 AST/ALT elevations had documented drug-induced liver injury on liver biopsy. In addition, one patient experienced a Grade 4 adverse event of drug-induced liver injury and another patient experienced 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).

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 in Table 2 (see section 4.2).

Bradycardia

Symptomatic bradycardia can occur with Alecensa. In the Phase I/II clinical trials (NP28673 and NP28761), there were 14 cases of sinus bradycardia (5.5%) and 7 cases of bradycardia (2.8%), some of which were symptomatic. None were severe or serious. Of 221 patients treated with Alecensa in studies NP28673 and NP28761 who had serial ECGs available, 20% had post-dose heart rates slower than 50 beats per minute (bpm). In study BO28984, cases of

bradycardia were reported in 11% of patients treated with Alecensa (see section 4.8, Table 3). Of the 144 patients treated with Alecensa for whom serial ECGs were available, 15% had heart rates of less than 50 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 in Table 2 (see section 4.2).

Severe myalgia and creatine phosphokinase (CPK) elevation

Myalgia/musculoskeletal pain were reported very commonly in patients treated with Alecensa in clinical trials. In Phase I/II clinical trials (NP28673 and NP28761), myalgia/musculoskeletal pain was reported in 30.8% of patients treated with Alecensa. The majority of these events were Grade 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 in studies NP28673 and NP28761, and ten of these patients (5.0%) had Grade 3 elevations. Dose modifications for elevation of CPK occurred in 4.0% of patients.

Myalgia or musculoskeletal pain occurred in 23% of patients treated with Alecensa in Phase III (BO28984). No patient experienced a Grade ≥3 adverse event, discontinued study treatment or had dose modifications due to these adverse events. CPK elevations occurred in 37% of 129 Alecensa-treated patients with available CPK laboratory data in study BO28984. Grade 3 elevations of CPK occurred in 3.1% of patients and dose modifications for elevation of CPK occurred in 1.3% of patients treated with Alecensa.

Median time to Grade 3 CPK elevation was 14 days in the pivotal Phase I/II trials (NP28673 and NP28761). Median time to Grade 3 CPK elevation was 27.5 days in the pivotal Phase III clinical trial (BO28984).

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).

Haemolytic anaemia

Haemolytic anaemia has been reported with Alecensa (see section 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 30 (11.9%) patients exposed to Alecensa in the Phase I/II clinical trials and in 8 (5.3%) patients treated with Alecensa in the Phase III trial.

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.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on alectinib

CYP3A inducers

Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong cytochrome p450 (CYP) isozyme 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-glycoprotein (P-gp). Alectinib and M4 are not substrates of breast cancer resistance protein (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.

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*.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Alecensa may cause fetal harm when administered to a pregnant woman (see section 5.3). 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 section 5.3), 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.

Pregnancy (Category D)

Based on animal studies and its mechanism of action, Alecensa may cause fetal harm if taken during pregnancy (see section 5.3). No clinical studies of Alecensa in pregnant women have been performed.

Advise patients that they must inform their healthcare provider of a known or suspected pregnancy. Advise a pregnant woman of the potential harm to the fetus.

The use of Alecensa during labour and delivery has not been established.

Breastfeeding

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.

Fertility

No fertility-specific studies of alectinib in animals have been performed. No adverse effects on male and female reproductive organs were observed in general toxicology studies (see section 5.3).

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.

Alecensa has minor influence on the ability to drive and use machines. 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).

4.8 Undesirable effects

Summary of the safety profile

For the clinical development program of Alecensa as a whole, an estimated total of 928 patients have received Alecensa and 203 patients have received blinded Alecensa. The safety of Alecensa has been evaluated in two Phase I/II clinical trials (NP28673 and NP28761) in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with the recommended dose of 600 mg twice daily (see section 5.1). 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 safety of Alecensa was also evaluated in 152 patients with ALK-positive NSCLC treated with a dose of 600 mg twice daily in the Phase III clinical trial BO28984. The median duration of exposure to Alecensa was 17.9 months

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

Tabulated list of adverse reactions

Table 3 lists the adverse drug reactions (ADRs) occurring in patients who received Alecensa in pivotal clinical trials.

ADRs from clinical trials are listed by MedDRA system organ class. The corresponding frequency category for each ADR is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

Table 3: ADRs occurring in patients treated with Alecensa in pivotal Phase II clinical trials (NP28673 and NP28761) and Phase III clinical trial BO28984

Adverse Drug Reactions (MedDRA)	**Alecensa N=253 (NP28673 and NP28761)/N=152 (BO28984)[#]**		
System Organ Class	**All Grades (%)**	**Frequency category (All Grades)**	**Grade 3-4 (%)**
Gastrointestinal disorders			
Constipation	36	very common	0
Nausea	22	very common	0.7[#]
Diarrhoea	18	very common	1.2
Vomiting	13	very common	0.4
Stomatitis[1]	3.3[#]	common	0[#]
General disorders and administration site conditions			
Oedema[2]	34	very common	0.8
Musculoskeletal and connective tissue disorders			
Myalgia[3]	31	very common	1.2
Increased blood creatine phosphokinase	13	very common	3.6
Hepatobiliary disorders			
Increased bilirubin[4]	21[#]	very common	3.3[#]
Increased AST	16	very common	5.3[#]
Increased ALT	15[#]	very common	4.6[#]
Drug-induced liver injury[5]	0.8	uncommon	0.8
Skin and subcutaneous tissue disorders			
Rash[6]	20	very common	0.7[#]
Photosensitivity reaction	12	very common	0.7[#]
Blood and lymphatic system disorders			
Anaemia[7]	20[#]	very common	4.6[#]
Eye disorders			
Vision disorders[8]	12	very common	0

Adverse Drug Reactions (MedDRA)	**Alecensa N=253 (NP28673 and NP28761)/N=152 (BO28984)[#]**		
System Organ Class	**All Grades (%)**	**Frequency category (All Grades)**	**Grade 3-4 (%)**
Cardiac disorders			
Bradycardia[9]	11[#]	very common	0
Investigations			
Weight increased[#]	9.9[#]	common	0.7[#]
Renal and urinary disorders			
Increased blood creatinine	7.9[#]	common	1.3[#*]
Acute kidney injury[#]	2.6[#]	common	2.6[#*]
Nervous System Disorders			
Dysgeusia[#10]	3.3[#]	common	0.7[#]
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease/pneumonitis	1.3[#]	common	0.4

[#] Event and/or rate reported in study BO28984 (N=152 patients treated with Alecensa); remainder of events and/or rates reported in trials NP28761, NP28673 (N=253 patients treated with Alecensa)

[*] Includes one Grade 5 event

[1] Includes cases of stomatitis and mouth ulceration

[2] Includes cases of peripheral oedema, oedema, generalised oedema, eyelid oedema, periorbital oedema

[3] Includes cases of myalgia and musculoskeletal pain

[4] Includes cases of increased blood bilirubin, hyperbilirubinaemia and increased bilirubin conjugated

[5] Includes one patient with reported MedDRA term of drug-induced liver injury as well as one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy.

[6] Includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic and rash macular

[7] Includes cases of anaemia and haemoglobin decreased

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

[9] Includes cases of bradycardia and sinus bradycardia

[10] Includes cases of dysgeusia and hypogeusia

Post Marketing

The adverse drug reaction of increased alkaline phosphatase was reported with Alecensa in the post-marketing setting. Cases of increased alkaline phosphatase have been reported in Alecensa clinical trials (7.5% in patients treated with Alecensa in pivotal phase II clinical trials, NP28761 and NP28673).

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

Description of selected adverse drug reactions

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 trial (BO28984) and the pivotal phase I/II trials (NP28673 and NP28761); however, relevant differences between studies are described in section 4.4.

Laboratory Abnormalities

Table 4 summarises the most common treatment-emergent shifts in key laboratory abnormalities occurring in patients who received Alecensa in phase II clinical trials (NP28673 and NP28761) and phase III clinical trial BO28984.

Table 4: Alecensa treatment-emergent shifts in key laboratory abnormalities

Parameter	**Alecensa N=250*/N=152#**	
	All Grades (%)	**Grade 3 -4° (%)**
Chemistry		
Increased AST	53*	6.2#
Increased blood bilirubin	53#	5.5#
Increased blood CPK[a]	46*	5.0*
Increased ALT	40#	6.1#
Increased blood creatinine**	38#	3.4#
Haematology		
Decreased haemoglobin	62#	6.8#

AST=aspartate aminotransferase; CPK=creatine phosphokinase; ALT=alanine aminotransferase
Note: Laboratory abnormalities were based on the normal ranges of the NCI CTCAE

* Rate reported in NP28761 and NP28673 studies; N=219 for CPK.

\# Rate reported in study BO28984; Patients with missing baseline and/or no post-baseline lab assessments were excluded from analyses; N=147 for blood creatinine, ALT and haemoglobin; N=145 for AST; N=146 for blood bilirubin.

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

° No Grade 5 laboratory abnormalities were reported.

Reporting of suspected adverse reactions

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

professionals are asked to report any suspected adverse reactions (https://nzphvc.otago.ac.nz/reporting/).

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 more than 99% bound to plasma proteins and haemodialysis is likely to be ineffective in the treatment of overdose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-neoplastic agents, protein kinase inhibitor; ATC code: L01XE36.

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 anti-tumour activity and prolonged survival.

Clinical efficacy and safety

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 [BO28984 (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.

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 5 and the Kaplan-Meier curves for investigator and Independent Review Committee (IRC)-assessed PFS are shown in Figures 1 and 2.

Table 5. Summary of efficacy results from study BO28984 (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 (%)	102 (68%)	62 (41%)
Median (months)	11.1	NE
[95% CI]	[9.1; 13.1]	[17.7; NE]
HR	0.47	
[95% CI]	[0.34, 0.65]	
Stratified log-rank p-value	p <0.0001	
Secondary efficacy parameters		
PFS (IRC)*		
Number of patients with event n (%)	92 (61%)	63 (41%)
Median (months)	10.4	25.7
[95% CI]	[7.7; 14.6]	[19.9; NE]
HR	0.50	
[95% CI]	[0.36; 0.70]	
Stratified log-rank p-value	p < 0.0001	
Time to CNS progression (IRC)*		

	Crizotinib N=151	Alecensa N=152
(without prior systemic PD**)		
Number of patients with event n (%)	68 (45%)	18 (12%)
Cause-Specific HR	0.16	
[95% CI]	[0.10; 0.28]	
Stratified log-rank p-value	p < 0.0001	
12-month cumulative incidence of CNS progression (IRC)	41.4%	9.4%
% (95% CI)	[33.2; 49.4]	[5.4; 14.7]
ORR (INV)*, ***		
Responders n (%)	114 (75.5%)	126 (82.9%)
[95% CI]	[67.8; 82.1]	[76.0; 88.5]
Overall survival*		
Number of patients with event n (%)*	40 (27%)	35 (23%)
Median (months)	NE	NE
[95% CI]	[NE; NE]	[NE; NE]
HR	0.76	
[95% CI]	[0.48; 1.20]	
Duration of response (INV)	N=114	N=126
Median (months)	11.1	NE
95 % CI	[7.9; 13.0]	[NE; NE]
CNS-ORR in patients with measurable CNS metastases at baseline	N=22	N=21
CNS responders n (%)	11 (50.0%)	17 (81.0%)
[95% CI]	[28.2; 71.8]	[58.1; 94.6]
CNS-CR n (%)	1 (5%)	8 (38%)
CNS-DOR , median (months)	5.5	17.3
95% CI	[2.1, 17.3]	[14.8, NE]
CNS-ORR in patients with measurable and non-measurable CNS metastases at baseline (IRC)	N=58	N=64
CNS responders n (%)	15 (25.9%)	38 (59.4%)
[95% CI]	[15.3%; 39.0%]	[46.4%; 71.5%]
CNS-CR n (%)	5 (9%)	29 (45%)
CNS-DOR , median (months)	3.7	NE
95% CI	[3.2, 6.8]	[17.3, NE]

* Key secondary endpoints part of the hierarchical testing

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

	Crizotinib N=151	Alecensa N=152

*** 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 1: Kaplan Meier Plot of INV-Assessed PFS in study BO28984 (ALEX)

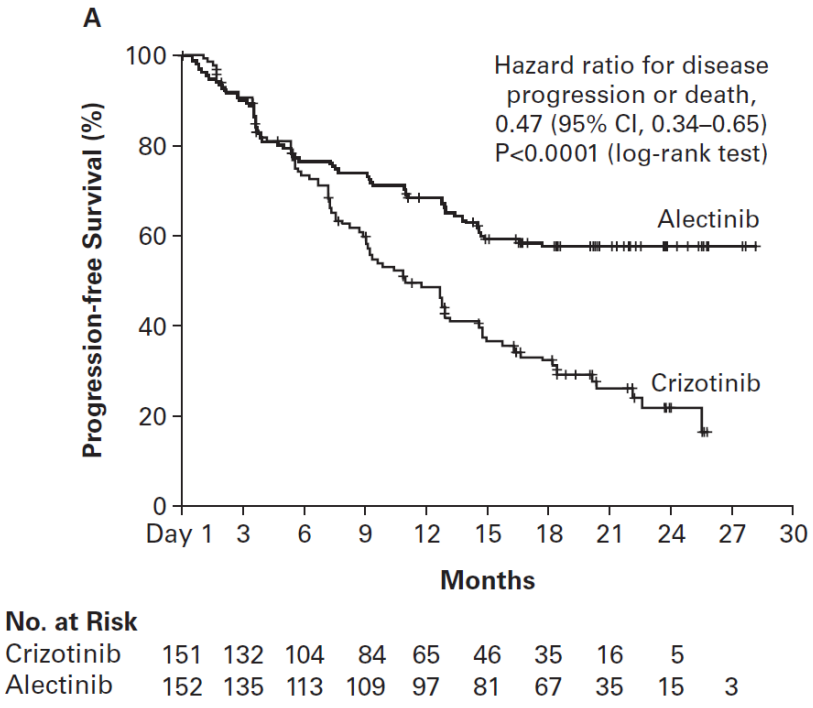
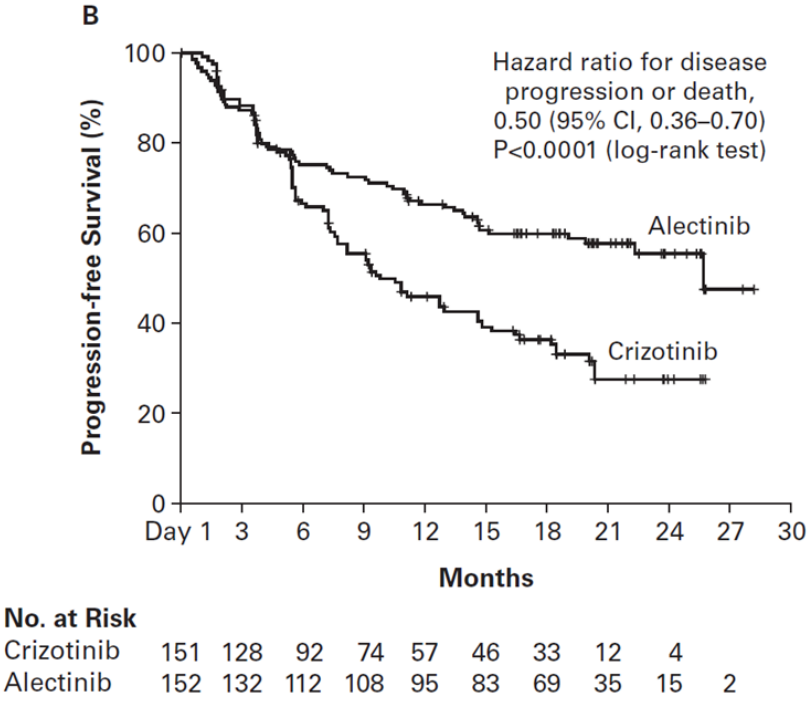


Figure 2: Kaplan Meier Plot of IRC Assessed PFS in study BO28984 (ALEX)



Crizotinib pre-treated patients

The safety and efficacy of Alecensa in ALK-positive NSCLC patients pre-treated with crizotinib were studied in two Phase I/II clinical trials (NP28673 and NP28761).

Study NP28673

Study NP28673 was a Phase I/II single arm, international, multicentre study conducted in patients with ALK-positive advanced NSCLC who have previously progressed on crizotinib. In addition to crizotinib, patients may have received previous treatment with chemotherapy. A total of 138 patients were included in the phase II part of the study and received Alecensa orally at the recommended dose of 600 mg twice daily.

The primary endpoint was to evaluate the efficacy of Alecensa by objective response rate (ORR) as per central independent review committee (IRC) assessment using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the overall population (with and without prior exposure of cytotoxic chemotherapy treatments). The co-primary endpoint was to evaluate the ORR as per central IRC assessment using RECIST 1.1 in patients with prior exposure of cytotoxic chemotherapy treatments.

Patient demographics were consistent with that of a NSCLC ALK positive population. The demographic characteristics of the overall study population were 67% Caucasian, 26% Asian, 56% females and the median age was 52 years. The majority of patients had no history of smoking (70%). The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 or 1 in 91% of patients and 2 in 9% of patients. At the time of entry in the

study, 99% of patients had stage IV disease, 61% had brain metastases and 96% of tumours were classified as adenocarcinoma. Among patients included in the study, 20% had previously progressed on crizotinib treatment only, and 80% had previously progressed on crizotinib and chemotherapy treatment.

Study NP28761

Study NP28761 was a Phase I/II single arm, multicentre study conducted in patients with ALK-positive advanced NSCLC who have previously progressed on crizotinib treatment. In addition to crizotinib, patients may have received previous treatment with chemotherapy. A total of 87 patients were included in the phase II part of the study and received Alecensa orally at the recommended dose of 600 mg twice daily.

The primary endpoint was to evaluate the efficacy of Alecensa by ORR as per central IRC assessment using RECIST 1.1.

Patient demographics were consistent with that of a NSCLC ALK positive population. The demographic characteristics of the overall study population were 84% Caucasian, 8% Asian, 55% females and a median age of 54 years. The majority of patients had no history of smoking (62%). The ECOG performance status at baseline was 0 or 1 in 90% of patients and 2 in 10% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 60% had brain metastases and 94% of tumours were classified as adenocarcinoma. Among patients included in the study, 26% had previously progressed on crizotinib treatment only, and 74% had previously progressed on crizotinib and chemotherapy treatment.

Table 6: Efficacy results from studies NP28673 and NP28761

	NP28673 Alecensa 600 mg twice daily	**NP28761 Alecensa 600 mg twice daily**
Median duration of follow-up (months)	21 (range 1 – 30)	17 (range 1 – 29)
Primary efficacy parameters		
ORR (IRC) in RE population Responders N (%) [95% CI]	N=122[a] 62 (50.8%) [41.6%, 60.0%]	N=67[b] 35 (52.2%) [39.7%, 64.6%]
ORR (IRC) in patients pre-treated with chemotherapy Responders N (%) [95% CI]	N = 96 43 (44.8%) [34.6%, 55.3%]	
Secondary efficacy parameters		
DOR (IRC) Number of patients with events N (%) Median (months) [95% CI]	N=62 36 (58.1%) 15.2 [11.2, 24.9]	N=35 20 (57.1%) 14.9 [6.9, NE]
PFS (IRC) Number of patients with events N (%) Median duration (months) [95% CI]	N=138 98 (71.0%) 8.9 [5.6, 12.8]	N=87 58 (66.7%) 8.2 [6.3, 12.6]

CI=confidence interval; DOR=duration of response; IRC=independent review committee; NE=not estimable; ORR=objective response rate; PFS=progression free survival; RE=response evaluable

[a] 16 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population

[b] 20 patients did not have measurable disease at baseline according to the IRC and were not included in the IRC response evaluable population

A summary of the pooled analysis of the Central Nervous System (CNS) endpoints based on RECIST (IRC) performed on patients with measurable CNS lesions at baseline (N=50) included in phase II studies NP28761 and NP28673 is presented in Table 7.

Table 7: Summary of the pooled analysis of CNS endpoints from studies NP28673 and NP28761

CNS Parameters (NP28673 and NP28761)	Alecensa 600 mg twice daily
Patients with measurable CNS lesions at baseline	N=50
CNS ORR (IRC) Responders (%) [95% CI] Complete response Partial response	 32 (64.0%) [49.2%, 77.1%] 11 (22.0%) 21 (42.0%)
CNS DCR (IRC) CR+PR+SD[a] [95% CI]	 45 (90.0%) [78.2%, 96.7%]
CNS DOR (IRC) Number of patients with events (%) Median (months) [95%CI]	N=32 18 (56.3%) 11.1 [7.6, NE]

CI=confidence interval; CR=complete response; DCR= disease control rate; DOR=duration of response; IRC=independent review committee; NE= not estimable ; ORR=objective response rate; PR=partial response; SD=stable disease

[a] DCR calculated including all patients who achieved a Best Overall Response (BOR) of SD (minimum duration of 5 weeks as per IRC Charter).

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 8.

Table 8: 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 ($AUC_{0\text{-}inf}$ 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-gp, BCRP, OATP 1B1 or OATP 1B3. 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.

Biotransformation

In vitro studies showed that alectinib is mainly metabolised by 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-labelled alectinib demonstrated that alectinib and M4 are the main circulating moieties in plasma, constituting 76% of the total radioactivity.

Elimination

Following administration of a single oral dose of ^{14}C-labelled 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 (NP28673 and NP28761) was undertaken to characterise the PK of alectinib and M4 in special populations.

Effects of age, body weight, race and gender

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

Hepatic impairment

Elimination of alectinib is predominantly through hepatic metabolism. Mild hepatic impairment had no clinically meaningful effect on the systemic exposure of alectinib and M4. 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.

Following administration of a single oral dose of 300 mg alectinib in subjects with moderate (Child-Pugh B) hepatic impairment, the combined exposure of alectinib and M4 was modestly increased compared with matched healthy subjects (geometric mean ratio [90% confidence interval] for moderate/healthy: C_{max}: 1.16 [0.786 – 1.72], AUC_{inf}: 1.36 [0.947 – 1.96)]. Administration of a single oral dose of 300 mg alectinib in subjects with severe (Child-Pugh C) hepatic impairment resulted in a greater increase in the combined exposure of alectinib and M4 compared with matched healthy subjects (geometric mean ratio [90% confidence interval] for severe/healthy: C_{max}: 0.981 [0.517 – 1.86], AUC_{inf}: 1.76 [0.984 – 3.15]).

No dose adjustments are required for Alecensa in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg).

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.

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 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.

Effects on fertility

No fertility-specific studies of alectinib in animals have been performed. No adverse effects on male and female reproductive organs were observed in general toxicology studies conducted in rats and monkeys at exposures equal to or greater than 2.6 and 0.5 fold, respectively, of the human exposure measured by AUC at the recommended dose of 600 mg twice daily.

Reproductive toxicity

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).

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.

Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with alectinib doses of ≥ 27 mg/kg/day ($AUC_{0\text{-}24h}$ 38200 ng.h/mL) resulted in changes in the growing teeth and bones. Findings in teeth included discolouration 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 ($AUC_{0\text{-}24h}$ 13900 ng.h/mL).

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 (E171)
Carnauba wax
Maize starch
Hypromellose

Printing ink

Iron oxide red (E172)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)
Carnauba wax
Shellac
Glyceryl monooleate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminum foil blister sealed with an aluminum lidding foil containing 8 capsules per blister. Pack size: 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.

7 MEDICINE SCHEDULE

Prescription

8 SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND

Medical enquiries: 0800 656 464

9 DATE OF FIRST APPROVAL

21 December 2017

10 DATE OF REVISION OF THE TEXT

31 August 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Shelf life extension to 5 years