ALECENSA

Alectinib

Capsules 150 mg

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect
Each hard capsule contains 33.7 mg lactose (as monohydrate) and 6 mg sodium (as sodium laurilsulfate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White to yellowish white, size 1 hard capsules, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant Treatment of Resected ALK-Positive Non-Small Cell Lung Cancer (NSCLC)

Alecensa is indicated as adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥ 4 cm or node positive), as detected by a validated test.

Treatment of Advanced Non-Small Cell Lung Cancer

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

Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

4.2 Posology and method of administration

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

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

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

Patients with underlying severe hepatic impairment (Child-Pugh C) should receive a starting dose of 450 mg taken twice daily with food (total daily dose of 900 mg).
Duration of treatment

Adjuvant treatment of resected NSCLC
Treatment with Alecensa should be continued until disease recurrence, unacceptable toxicity or for 2 years.

Treatment of advanced NSCLC
Treatment with Alecensa should be continued until disease progression or unacceptable toxicity.

Delayed or missed doses
If a planned dose of Alecensa is missed, patients can make up that dose unless the next dose is due within 6 hours. Patients should not take two doses at the same time to make up for a missed dose. If vomiting occurs after taking a dose of Alecensa, patients should take the next dose at the scheduled time.

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

Dose modification advice is provided in Tables 1 and 2 below.

Table 1 Dose reduction schedule

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

Table 2 Dose modification advice for specified adverse drug reactions (see sections 4.4 and 4.8)

CTCAE grade	**Alecensa treatment**
ILD/pneumonitis of any severity grade	Immediately interrupt and permanently discontinue Alecensa if no other potential causes of ILD/pneumonitis have been identified.
ALT or AST elevation of Grade ≥ 3 (> 5times 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).

CTCAE grade	**Alecensa treatment**
ALT or AST elevation of Grade ≥ 2 (> 3 times ULN) with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis	Permanently discontinue Alecensa.
Bradycardia[a] Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated)	Temporarily withhold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products. If a contributing concomitant medicinal product 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 medicinal product is identified, or if contributing concomitant medicinal products 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 medicinal product is identified. If a contributing concomitant medicinal product 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 the same dose.
CPK elevation > 10 times ULN or second occurrence of CPK elevation of > 5 times ULN	Temporarily withhold until recovery to baseline or to ≤ 2.5 times ULN, then resume at reduced dose as per Table 1.
Haemolytic anaemia with haemoglobin of < 10 g/dL (Grade ≥ 2)	Temporarily withhold until resolution, then resume at reduced dose (see Table 1).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; CTCAE = NCI Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; ULN = upper limit of normal
[a] Heart rate less than 60 beats per minute (bpm).

Special populations

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 taken twice daily (total dose of 900 mg) (see section 5.2). For all patients with hepatic impairment, appropriate monitoring (e.g. markers of liver function) is advised, see section 4.4.

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

Elderly (≥ 65 years)
The limited data on the safety and efficacy of Alecensa in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section 5.2). There are no available data on patients over 80 years of age.

Paediatric population
The safety and efficacy of Alecensa in children and adolescents below 18 years of age have not been established. No data are available.

Extreme body weight (>130 kg)
Although pharmacokinetic (PK) simulations for Alecensa do not indicate a low exposure in patients with extreme body weight (i.e. >130 kg), alectinib is widely distributed and clinical studies for alectinib enrolled patients within a range of body weights of 36.9–123 kg. There are no available data on patients with body weight above 130 kg.

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 (see section 5.2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Interstitial lung disease (ILD)/pneumonitis
Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa (see section 4.8). Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alecensa should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified (see section 4.2).

Hepatotoxicity
Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 5 times the upper limit of normal (ULN) as well as bilirubin elevations of more than 3 times the ULN occurred in patients in pivotal clinical trials with Alecensa (see section 4.8). The majority of these events occurred during the first 3 months of treatment. In the pivotal Alecensa clinical trials it was reported that three patients with Grade 3-4 AST/ALT elevations had drug induced liver injury.

Concurrent elevations in ALT or AST greater than or equal 3 times the ULN and total bilirubin greater than or equal 2 times the ULN, with normal alkaline phosphatase, occurred in one patient treated in Alecensa clinical trials.

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

Severe myalgia and creatine phosphokinase (CPK) elevation
Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alecensa, including Grade 3 events (see section 4.8).

Elevations of CPK occurred in pivotal trials with Alecensa, including Grade 3 events (see section 4.8). Median time to Grade ≥ 3 CPK elevation was 15 days across clinical trials (BO40336, BO28984, NP28761, NP28673).

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness. CPK levels should be assessed every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, Alecensa should be withheld, then resumed or dose reduced (see section 4.2).

Bradycardia
Symptomatic bradycardia can occur with Alecensa (see section 4.8). Heart rate and blood pressure should be monitored as clinically indicated. Dose modification is not required in case of asymptomatic bradycardia (see section 4.2). If patients experience symptomatic bradycardia or life-threatening events, concomitant medicinal products known to cause bradycardia, as well as anti-hypertensive medicinal products should be evaluated and Alecensa treatment should be adjusted as described in Table 2 (see sections 4.2 and 4.5, 'P-gp substrates' and 'BCRP substrates').

Haemolytic anaemia
Haemolytic anaemia has been reported with Alecensa (see section 4.8). If haemoglobin concentration is below 10 g/dL and haemolytic anaemia is suspected, Alecensa should be withheld and appropriate laboratory testing should be initiated. If haemolytic anaemia is confirmed, Alecensa should be resumed at a reduced dose upon resolution as described in Table 2 (see section 4.2).

Gastrointestinal perforation
Cases of gastrointestinal perforations 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 recognized risk of gastrointestinal perforation) treated with alectinib. Discontinuation of Alecensa in patients who develop gastrointestinal perforation should be considered. Patients should be informed of the signs and symptoms of gastrointestinal perforations and advised to consult rapidly in case of occurrence.

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

Women of child-bearing potential
Alecensa may cause foetal harm when administered to a pregnant woman. Female patients of child-bearing potential receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa (see sections 4.5, 4.6 and 5.3).

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

Sodium content
This medicinal product contains 48 mg sodium per daily dose (1200 mg), equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

CYP3A inducers
Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib reduced alectinib C_{max}, and AUC_{inf} by 51% and 73% respectively and increased M4 C_{max}-and AUC_{inf} 2.20 and 1.79-fold respectively. The effect on the combined exposure of alectinib and M4 was minor, reducing C_{max} and AUC_{inf} by 4% and 18%, respectively. Based on the effects on the combined exposure of alectinib and M4, no dose adjustments are required when Alecensa is co-administered with CYP3A inducers. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum)).

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 increased alectinib exposure C_{max} and AUC_{inf} by 1.18 and 1.75-fold respectively, and reduced M4 C_{max} and AUC_{inf} by 71% and 25% respectively. The effect on the combined exposure of alectinib and M4 was minor, reducing C_{max} by 7% and increasing AUC_{inf} 1.36-fold. Based on the effects on the combined exposure of alectinib and M4, no dose adjustments are required when Alecensa is co-administered with CYP3A inhibitors. Appropriate monitoring is recommended for patients taking concomitant strong CYP3A inhibitors (including, but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole nefazodone, grapefruit or Seville oranges).

Medicinal products that increase gastric pH
Multiple doses of esomeprazole, a proton pump inhibitor, 40 mg once daily, 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 medicinal products which raise gastric pH (e.g. H2 receptor antagonists or antacids).

Effect of transporters on alectinib disposition
M4 is a substrate of P-glycoprotein (P-gp). As alectinib inhibits P-gp, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 exposure.

Effects of alectinib on other medicinal products

CYP substrates
In vitro, alectinib and M4 show weak time-dependent inhibition of CYP3A4, and alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations.

Multiple doses of 600 mg alectinib had no influence on the exposure of midazolam (2 mg), a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates.

A risk for induction of CYP2B6 and pregnane X receptor (PXR) regulated enzymes apart from CYP3A4 cannot be completely excluded. The effectiveness of concomitant administration of oral contraceptives may be reduced.

P-gp substrates
In vitro, alectinib and its major active metabolite M4 are inhibitors of the efflux transporter P-gp. Therefore, alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of P-gp. When Alecensa is co-administered with P-gp substrates (e.g., digoxin, dabigatran etexilate, topotecan, sirolimus, everolimus, nilotinib and lapatinib), appropriate monitoring is recommended.

Breast cancer resistance protein (BCRP) substrates
In vitro, alectinib and M4 are inhibitors of the efflux transporter BCRP. Therefore, alectinib and M4 may have the potential to increase plasma concentrations of co-administered substrates of BCRP. When Alecensa is co-administered with BCRP substrates (e.g., methotrexate, mitoxantrone, topotecan and lapatinib), appropriate monitoring is recommended.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Women of childbearing potential must be advised to avoid pregnancy while on Alecensa. Female patients of child-bearing potential receiving Alecensa must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa (see sections 4.4 and 4.5).

Pregnancy
There are no or limited amount of data from the use of alectinib in pregnant women. Based on its mechanism of action, alectinib may cause foetal harm when administered to a pregnant woman. Studies in animals have shown reproductive toxicity (see section 5.3).

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

Breast-feeding
It is unknown whether alectinib and/or its metabolites are excreted in human milk. A risk to the newborn/infant cannot be excluded. Mothers should be advised against breast-feeding while receiving Alecensa.

Fertility
No fertility studies in animals have been performed to evaluate the effect of alectinib. 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

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

The data described below reflect exposure to Alecensa in 533 patients with resected or advanced ALK-positive NSCLC. These patients received Alecensa at the recommended dose of 600 mg twice daily in pivotal clinical trials for adjuvant treatment of resected NSCLC (BO40336, ALINA) or for

treatment of advanced NSCLC (BO28984, ALEX; NP28761; NP28673). See section 5.1 for further information on clinical trial participants.

In BO40336 (ALINA; N=128), the median duration of exposure to Alecensa was 23.9 months. In BO28984 (ALEX; N=152) the median duration of exposure to Alecensa was 28.1 months, In the phase II clinical trials (NP28761, NP28673; N=253), the median duration of exposure to Alecensa was 11.2 months.
The most common adverse drug reactions (ADRs) (≥ 20%) were constipation, myalgia, oedema, anaemia, rash, increased bilirubin, increased ALT and increased AST.

Tabulated list of adverse drug reactions
Table 3 lists the ADRs occurring in patients who received Alecensa across clinical trials (BO40336, BO28984, NP28761, NP28673).

The ADRs listed in Table 3 are presented by system organ class and frequency categories, defined using 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). Within each system organ class, undesirable effects are presented in order of decreasing frequency and severity. Within the same frequency and severity grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3 ADRs reported in Alecensa clinical trials (BO40336, BO28984, NP28761, NP28673; N=533)

System organ class ADRs (MedDRA)	**Alecensa N=533**	
	Frequency category (all grades)	**Frequency category (grades 3-4)**
Blood and lymphatic system disorders		
Anaemia[1)]	Very common	Common
Haemolytic anaemia[2)]	Common	-*
Nervous system disorders		
Dysgeusia[3)]	Common	Uncommon
Eye disorders		
Vision disorders[4)]	Common	-*
Cardiac disorders		
Bradycardia[5)]	Very common	-*
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease / pneumonitis	Common	Uncommon
Gastrointestinal disorders		
Diarrhoea	Very common	Uncommon
Vomiting	Very common	Uncommon
Constipation	Very common	Uncommon
Nausea	Very common	Uncommon
Stomatitis[6)]	Common	Uncommon
Hepatobiliary disorders		
Increased AST	Very common	Common
Increased ALT	Very common	Common
Increased bilirubin[7)]	Very common	Common
Increased alkaline phosphatase	Very Common	Uncommon
Drug-induced liver injury[8)]	Uncommon	Uncommon
Skin and subcutaneous tissue disorders		
Rash[9)]	Very common	Common
Photosensitivity	Common	Uncommon

System organ class ADRs (MedDRA)	Alecensa N=533	
	Frequency category (all grades)	**Frequency category (grades 3-4)**
Musculoskeletal and connective tissues disorders		
Myalgia[10)]	Very common	Uncommon
Increased blood creatine phosphokinase	Very common	Common
Renal and urinary disorders		
Acute kidney injury	Uncommon	Uncommon**
Blood creatinine increased	Common	Uncommon**
General disorders and administration site conditions		
Oedema[11)]	Very common	Uncommon
Investigations		
Weight increased	Very common	Uncommon
Metabolism and Nutrition Disorders		
Hyperuricaemia[12)]	Common	-*

* No Grade 3-4 ADRs were observed.
** Includes one Grade 5 event (observed in the advanced NSCLC setting).
1) includes cases of anaemia, haemoglobin decreased and normochromic normocytic anaemia.
2) cases reported in study BO40336 (N=128).
3) includes cases of dysgeusia, hypogeusia, and taste disorder.
4) includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, diplopia, photophobia, and photopsia.
5) includes cases of bradycardia and sinus bradycardia.
6) includes cases of stomatitis and mouth ulceration.
7) includes cases of blood bilirubin increased, hyperbilirubinaemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased.
8) includes two patients 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.
9) includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic, rash macular, exfoliative rash, and rash erythematous.
10) includes cases of myalgia, musculoskeletal pain, and arthralgia.
11) includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema, localised oedema, peripheral swelling, face swelling, lip swelling, swelling, joint swelling and eyelid swelling.
12) includes cases of hyperuricaemia and increased blood uric acid.

Description of selected adverse drug reactions

Interstitial lung disease (ILD) / pneumonitis
Across clinical trials, ILD/pneumonitis occurred in 1.3% of patients treated with Alecensa, 0.4% of these cases were Grade 3 and treatment discontinuations due to ILD/pneumonitis occurred in 0.9% of patients. In the phase III clinical trial BO28984, Grade 3 or 4 ILD/pneumonitis was not observed in patients receiving Alecensa versus 2.0% of patients receiving crizotinib. There were no fatal cases of ILD in any of the clinical trials. Patients should be monitored for pulmonary symptoms indicative of pneumonitis (see sections 4.2 and 4.4).

Hepatotoxicity
Across clinical trials, three patients had a documented drug-induced liver injury (including two patients with the reported term drug-induced liver injury and one patient with reported Grade 4 increased AST and ALT who had documented drug-induced liver injury by liver biopsy). Adverse reactions of increased AST and ALT levels (22.7% and 20.1% respectively) were reported in patients treated with Alecensa across clinical trials. The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 3.0% and 3.2% of the patients for increased AST and ALT levels, respectively. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (reported for 2.3% and 3.6% of the patients, respectively) or dose reduction (1.7% and 1.5%, respectively). In 1.1%

and 1.3% of the patients, AST and ALT elevations, respectively, led to withdrawal from Alecensa treatment. Grade 3 or 4 ALT or AST elevations were each observed in 5% of patients receiving Alecensa versus 16% and 11% of patients receiving crizotinib in the phase III clinical trial BO28984.

Adverse reactions of bilirubin elevations were reported in 25.1% of the patients treated with Alecensa across clinical trials. The majority of the events were of Grade 1 and 2 intensity; Grade ≥ 3 events were reported in 3.4% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and the majority resolved upon dose modification. In 7.7% of patients, bilirubin elevations led to dose modifications and in 1.5% of patients, bilirubin elevations led to withdrawal from Alecensa treatment. In the phase III clinical trial BO28984, Grade 3 or 4 bilirubin elevations occurred in 3.9% of patients receiving Alecensa versus no patient receiving crizotinib.

Concurrent elevations in ALT or AST greater than or equal to three times the ULN and total bilirubin greater than or equal to two times the ULN, with normal alkaline phosphatase, occurred in one patient (0.2%) treated in Alecensa clinical trials.

Patients should be monitored for liver function including ALT, AST, and total bilirubin as outlined in section 4.4 and managed as recommended in section 4.2.

Bradycardia
Cases of bradycardia (11.1%) of Grade 1 or 2 have been reported in patients treated with Alecensa across clinical trials. No patients had events of Grade≥3 severity. There were 102 of 521 patients (19.6%) treated with Alecensa, for whom serial ECGs were available, had post-dose heart rate values below 50 beats per minute (bpm). In the phase III clinical trial BO28984 15% of patients treated with Alecensa had post-dose heart rate values below 50 bpm versus 21% of patients treated with crizotinib. Patients who develop symptomatic bradycardia should be managed as recommended in sections 4.2 and 4.4. No case of bradycardia led to withdrawal from Alecensa treatment.

Severe myalgia and CPK elevations
Cases of myalgia (34.9%) including myalgia events (24.0%), arthralgia (16.1%), and musculoskeletal pain (0.9%) have been reported in patients treated with Alecensa across clinical trials. The majority of events were Grades 1 or 2 and five patients (0.9%) had a Grade 3 event. Dose modifications of Alecensa treatment due to these adverse events were required for nine patients (1.7%); Alecensa treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 55.6% of 491 patients with CPK laboratory data available across clinical trials with Alecensa. The incidence of Grade ≥ 3 elevations of CPK was 5.5%. Median time to Grade ≥ 3 CPK elevation was 15 days across trials. Dose modifications for elevation of CPK occurred in 5.3% of patients; withdrawal from Alecensa treatment did not occur due to CPK elevations. In the clinical trial BO28984, severe arthralgia was reported in one patient (0.7%) in the alectinib arm and in two patients (1.3%) in the crizotinib arm. Grade ≥ 3 elevation of CPK was reported for 3.9% of patients receiving Alecensa and 3.3% of patients receiving crizotinib.

Haemolytic anaemia
Haemolytic anaemia has been observed in 3.1% of patients treated with Alecensa in the clinical trial setting. These cases were Grade 1 or 2 (non-serious) and did not lead to treatment discontinuation (see sections 4.2 and 4.4).

Gastrointestinal effects
Constipation (38.6%), nausea (17.4%), diarrhoea (17.4%) and vomiting (12.0%) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate severity; Grade 3 events were reported for diarrhoea (0.9%), nausea (0.4%), vomiting (0.2%), and constipation (0.4%). These events did not lead to withdrawal from Alecensa treatment. Median time to onset for constipation, nausea, diarrhoea, and/or vomiting events across clinical trials was 21 days. The events declined in frequency after the first month of treatment. In the phase III clinical trial BO28984, Grade 3 and 4 events of nausea, diarrhoea and constipation were reported in one patient each (0.7%) in the alectinib arm and the incidence of Grade 3 and 4 events of nausea, diarrhoea and vomiting was 3.3%, 2.0% and 3.3%, respectively, in the crizotinib arm.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-neoplastic agents, protein kinase inhibitor; ATC code: L01ED03.

Mechanism of action

Alectinib is a highly selective and potent ALK and rearranged during transfection (RET) tyrosine kinase inhibitor. In pre-clinical studies, inhibition of ALK tyrosine kinase activity led to blockage of downstream signalling pathways including signal transducer and activator of transcription 3 (STAT 3) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and induction of tumour cell death (apoptosis).

Alectinib demonstrated *in vitro* and *in vivo* activity against mutant forms of the ALK enzyme, including mutations responsible for resistance to crizotinib. The major metabolite of alectinib (M4) has shown similar *in vitro* potency and activity.
Based on preclinical data, alectinib is not a substrate of P-gp or BCRP, which are both efflux transporters in the blood brain barrier, and is therefore able to distribute into and be retained within the central nervous system.

Clinical efficacy and safety

Adjuvant treatment of resected ALK-positive NSCLC

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 (BO40336; ALINA). Eligible patients were required to have Stage IB (tumours ≥ 4 cm) - Stage 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 CE-marked ALK test, or centrally performed by the Ventana ALK (D5F3) immunohistochemistry (IHC) assay.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with Stage IB (tumours ≥ 4 cm) – IIIA NSCLC according to the 7th Edition UICC/AJCC staging criteria:

Tumour size ≥ 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary.

The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients were randomised (1:1) to receive Alecensa or platinum-based chemotherapy following tumour resection. Randomisation was stratified by race (Asian and non-Asian) and stage of disease (IB, II and IIIA). Alecensa was administered at the recommended oral dose of 600 mg twice daily for a total of 2 years, or until disease recurrence or unacceptable 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 versus time curve (AUC) 5 mg/mL/min or AUC 6 mg/mL/min.

The primary efficacy endpoint was disease-free survival (DFS) as assessed by the Investigator. DFS was defined as the time from 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), and 24% were ≥ 65 years old, 52% were female, 56% were Asian, 60% were never smokers, 53% had an 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 improvement in DFS for patients treated with Alecensa compared to patients treated with chemotherapy in the Stage II-IIIA and the Stage IB (≥ 4 cm) - 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.

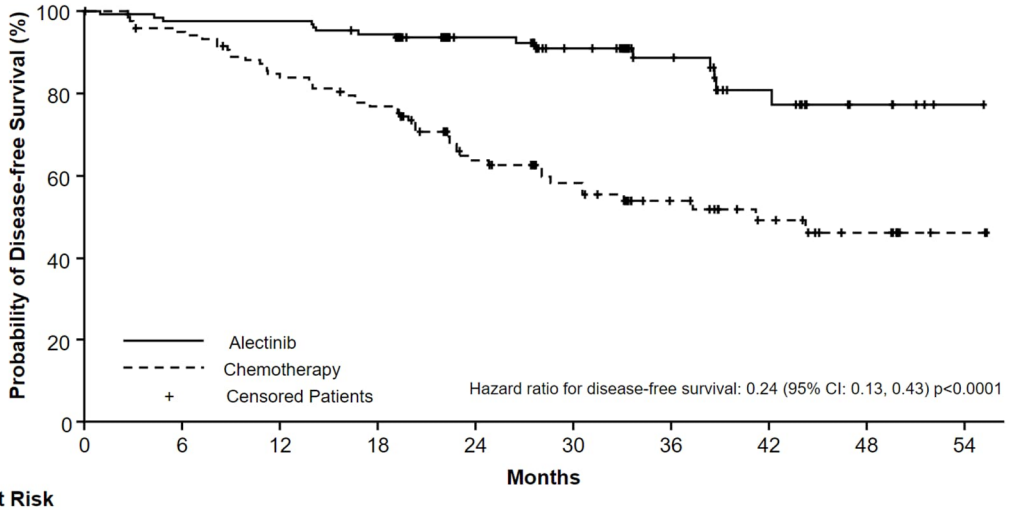
The DFS efficacy results are summarised in Table 4 and Figure 1.

Table 4 Investigator assessed DFS results in ALINA

Efficacy Parameter	**Stage II-IIIA**		**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 investigator assessed DFS in the ITT population



Patients at Risk										
Alectinib	130	123	123	118	74	55	39	22	10	3
Chemotherapy	127	112	98	89	55	41	27	18	11	2

Treatment of advanced ALK-positive NSCLC

Treatment-naïve patients

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 who were treatment naïve. Central testing for ALK protein expression positivity of tissue samples from all patients by Ventana anti-ALK (D5F3) immunohistochemistry 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.

Eastern Cooperative Oncology Group performance status ((ECOG PS) (0/1 vs. 2)), race (Asian vs. non-Asian), and central nervous system (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 Response Evaluation Criteria in Solid Tumors (RECIST) version 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 PS 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, demonstrating a statistically significant improvement in PFS by investigator. Efficacy data are summarised in Table 5 and the Kaplan-Meier curve for investigator assessed PFS is shown in Figure 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)*, **		
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]

	Crizotinib N=151	**Alecensa N=152**
CNS-ORR in patients with measurable CNS metastases at baseline	N=22	N=21
CNS responders n (%) [95% CI]	11 (50.0%) [28.2; 71.8]	17 (81.0%) [58.1; 94.6]
CNS-CR n (%)	1 (5%)	8 (38%)
CNS-DOR, median (months) [95% CI]	5.5 [2.1, 17.3]	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 (%) [95% CI]	15 (25.9%) [15.3; 39.0]	38 (59.4%) [46.4; 71.5]
CNS-CR n (%)	5 (9%)	29 (45%)
CNS-DOR, median (months) [95% CI]	3.7 [3.2, 6.8]	NE [17.3, NE]

* Key secondary endpoints part of the hierarchical testing

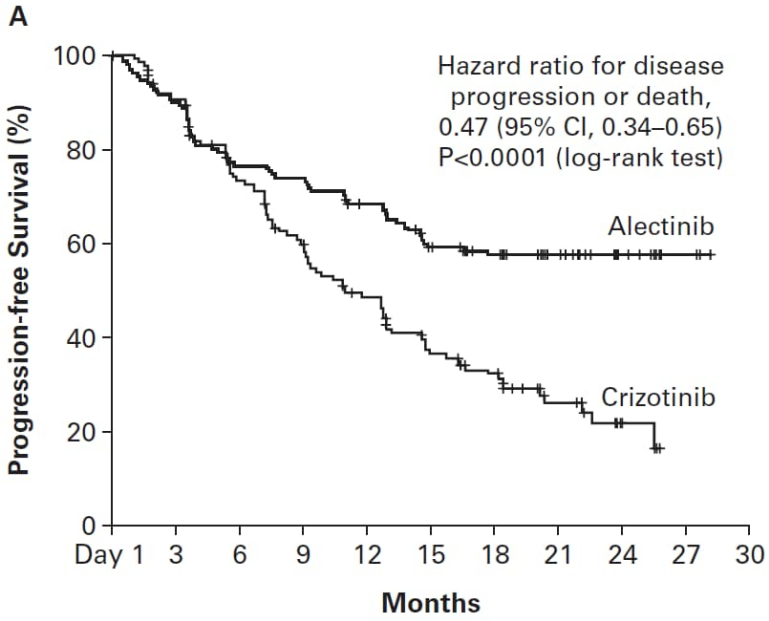
** Competing risk analysis of CNS progression, systemic progression and death as competing events

*** 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 PFS benefit was consistent for patients with CNS metastases at baseline (hazard ratio (HR) = 0.40, 95% confidence interval (CI): 0.25-0.64, median PFS for Alecensa = not estimable (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 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).

NP28673
Study NP28673 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 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 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. A lower confidence limit for the estimated ORR above the pre-specified threshold of 35% would achieve a statistically significant result.

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 ECOG PS at baseline was 0 or 1 in 90.6% of patients and 2 in 9.4% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 61% had brain metastases and in 96% of patients tumours were classified as adenocarcinoma. Among patients included in the study, 20% of the patients had previously progressed on crizotinib treatment only, and 80% had previously progressed on crizotinib and at least one 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 version 1.1. A lower confidence limit for the estimated ORR above the pre-specified threshold of 35% would achieve a statistically significant result.

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. The median age was 54 years. The majority of patients had no history of smoking (62%). The ECOG PS at baseline was 0 or 1 in 89.7% of patients and 2 in 10.3% of patients. At the time of entry in the study, 99% of patients had stage IV disease, 60% had brain metastases and in 94% of patients tumours were classified as adenocarcinoma. Among the patients included in the study, 26% of the patients had previously progressed on crizotinib treatment only, and 74% had previously progressed on crizotinib and at least one chemotherapy treatment.

The main efficacy results from studies NP28673 and NP28761 are summarised in Table 6. A summary of pooled analysis of CNS endpoints is presented in Table 7.

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

ORR results for studies NP28673 and NP28761 were consistent across subgroups of baseline patient characteristics such as age, gender, race, ECOG PS, CNS metastasis and prior chemotherapy use, especially when considering the small number of patients in some subgroups.

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 (%)	32 (64.0%)
[95% CI]	[49.2%, 77.1%]
Complete response	11 (22.0%)
Partial response	21 (42.0%)
CNS DOR (IRC)	N=32
Number of patients with events (%)	18 (56.3%)
Median (months)	11.1
[95%CI]	[7.6, NE]

CI = confidence interval; DOR = duration of response; IRC = independent review committee; ORR = objective response rate; NE = not estimable

5.2 Pharmacokinetic properties

The pharmacokinetic parameters for alectinib and its major active metabolite (M4) have been characterised in ALK-positive NSCLC patients and healthy subjects. Based on population pharmacokinetic analysis, the geometric mean (coefficient of variation %) steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for alectinib were approximately 665 ng/mL (44.3%), 572 ng/mL (47.8%) and 7430 ng*h/mL (45.7%), respectively. The geometric mean steady-state C_{max}, C_{min} and $AUC_{0\text{-}12hr}$ for M4 were approximately 246 ng/mL (45.4%), 222 ng/mL (46.6%) and 2810 ng*h/mL (45.9%), respectively.

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

Alectinib steady-state is reached within 7 days with continuous 600 mg twice daily dosing. The accumulation ratio for the twice-daily 600 mg regimen was approximately 6-fold. Population PK analysis supports dose proportionality for alectinib across the dose range of 300 to 900 mg under fed conditions.

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

Following a single oral administration of 600 mg with a high-fat, high-calorie meal, alectinib and M4 exposure was increased by around 3-fold relative to fasted conditions (see section 4.2).

Distribution
Alectinib and its major metabolite M4 are highly bound to human plasma proteins (>99%), independent of active substance 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 intravenous (IV) administration was 475 L, indicating extensive distribution into tissues.
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.

Biotransformation

In vitro metabolism studies showed that CYP3A4 is the main CYP isozyme mediating alectinib and its major metabolite M4 metabolism, and is estimated to contribute 40-50% of alectinib metabolism. Results from the human mass balance study demonstrated that alectinib and M4 were the main circulating moieties in plasma with 76% of the total radioactivity in plasma. The geometric mean Metabolite/Parent ratio at steady state is 0.399.

Metabolite M1b was detected as a minor metabolite from *in vitro* and in human plasma in healthy subjects. Formation of metabolite M1b and its minor isomer M1a is likely to be catalyzed by a combination of CYP isozymes (including isozymes other than CYP3A) and aldehyde dehydrogenase (ALDH) enzymes.

In vitro studies indicate that neither alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib did not inhibit OATP1B1/OATP1B3, OAT1, OAT3 or OCT2 at clinically relevant concentrations in vitro.

Elimination

Following administration of a single dose of ^{14}C-labeled alectinib administered orally to healthy subjects the majority of radioactivity was excreted in faeces (mean recovery 97.8%) with minimal excretion in urine (mean recovery 0.46%). In faeces, 84% and 5.8% of the dose was excreted as unchanged alectinib or M4, respectively.

Based on a population PK analysis, the apparent clearance (CL/F) of alectinib was 81.9 L/hour. The geometric mean of the individual elimination half-life estimates for alectinib was 32.5 hours. The corresponding values for M4 were 217 L/hour and 30.7 hours, respectively.

Pharmacokinetics in special populations

Renal impairment

Negligible amounts of alectinib and the active metabolite M4 are excreted unchanged in urine (< 0.2% of the dose). Based on a population pharmacokinetic analysis alectinib and M4 exposures were similar in patients with mild and moderate renal impairment and normal renal function. The pharmacokinetics of alectinib has not been studied in patients with severe renal impairment.

Hepatic impairment

As elimination of alectinib is predominantly through metabolism in the liver, hepatic impairment may increase the plasma concentration of alectinib and/or its major 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.

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. The range of body weights for patients enrolled in clinical studies is 36.9-123 kg. There are no available data on patients with extreme body weight (>130 kg) (see section 4.2).

5.3 Preclinical safety data

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

Mutagenicity
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.

Impairment of fertility
No fertility studies in animals have been performed to evaluate the effect of alectinib. No adverse effects on male and female reproductive organs were observed in general toxicology studies. These studies were 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 area under the curve (AUC), at the recommended dose of 600 mg twice daily.

Teratogenicity
Alectinib caused embryo-foetal toxicity in pregnant rats and rabbits. In pregnant rats, alectinib caused total embryo-foetal loss (miscarriage) at exposures 4.5-fold of the human AUC exposure and small foetuses with retarded ossification and minor abnormalities of the organs at exposures 2.7-fold of the human AUC exposure. In pregnant rabbits, alectinib caused embryo-foetal loss, small fetuses and increased incidence of skeletal variations at exposures 2.9-fold of the human AUC exposure at the recommended dose.

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

Target organs in both rat and monkey at clinically relevant exposures in the repeat-dose toxicology studies included, but were not limited to the erythroid system, gastrointestinal tract, and hepatobiliary system.

Abnormal erythrocyte morphology was observed at exposures equal or greater than 10-60% the human exposure by AUC at the recommended dose. Proliferative zone extension in gastrointestinal (GI) mucosa in both species was observed at exposures equal to or greater than 20-120% of the human AUC exposure at the recommended dose. Increased hepatic alkaline phosphatase (ALP) and direct bilirubin as well as vacuolation/degeneration/necrosis of bile duct epithelium and enlargement/focal necrosis of hepatocytes was observed in rats and/or monkeys at exposures equal to or greater than 20-30% of the human exposure by AUC at the recommended dose.

A mild hypotensive effect has been observed in monkeys at around clinically relevant exposures.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium lauryl sulfate
Hypromellose
Carboxymethylcellulose calcium
Lactose monohydrate
Hydroxypropylcellulose
Titanium dioxide (E171)
Magnesium stearate
Potassium chlorideCarrageenan
Carnauba wax
Corn starch

Printing ink:
White shellac
FD&C Blue No. 2 aluminium lake (E132)
Yellow iron oxide (E172)
Red iron oxide (E172)
Carnauba wax
Glyceryl monooleate
1-butanol
Dehydrated ethyl alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 30°C.

Bottles**:** Store in the original package to protect from light and keep the bottle tightly closed in order to protect from moisture.
Blisters: Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

HDPE bottle with a child-resistant closure and an integrated desiccant.
Pack size: 240 hard capsules.
Aluminium/aluminium blisters containing 8 hard capsules.
Pack size: 224 (4 packs of 56) hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Roche Pharmaceuticals (Israel) Ltd. P.O.B. 6391, Hod Hasharon, 4524079.

8. MARKETING AUTHORISATION NUMBER(S)

155-82-34552-00

9. MANUFACTURER

F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Medicine: keep out of reach of children

Revised on July 2024