ALECENSA®

in ALK+ advanced NSCLC as 1st-line treatment :[8]

- A wealth of evidence with consistent results in 3 phase-III trials[1-3]
- Over 72 000 patients treated worldwide[4,5]
- 5 years reimbursed in Belgium[6]
- The longest OS demonstrated vs. crizotinib, with 6/10 patients alive after 5 years[7]
- A well established long-term safety profile, without neurocognitive side-effects[5]

1. Hida T, et al. Lancet 2017;390:29–39;
2. Peters S, et al. N Eng J Med 2017;377:829–38;
3. Zhou C, et al. Lancet Respir Med 2019;7:437–46;
4. Data on file: Alecensa_FE 8.0_CDS 8.0
5. Dziadziuszko R. et al, ESMO Open 2022, Volume 7, Issue 6 (100612)
6. Moniteur Belge 2019:N210 $280408: available here https://www.ejustice.just.fgov.be/eli/arrete/2019/09/10/2019014506/moniteur
7. Mok T et al. Ann Oncol 2020; 31(8): 1056–1064.
8. SmPC Alecensa 08/2022 (https://www.e-bijsluiter.be/nl/bijsluiters/wetenschappelijk/6585/13610)

R.E.: Pharm. E. De Bruyne - M-BE-00002328 - created on 12/09/2023

Think positive, think ALECENSA® alectinib 150 mg capsules

CNK-code	Alecensa®		Ex-Factory Price Excl. VAT
3518-990	150 mg	224 caps	€ 5.459,32

NAME OF THE MEDICINAL PRODUCT Alecensa 150 mg hard capsules QUALITATIVE AND QUATANTITATIVE COMPOSITION Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib. For the full list of excipients, see section 6.1 of SmPC. 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. THERAPEUTIC INDICATIONS 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). Alecensa as monotherapy is indicated for the treatment of adult patients with ALKpositive advanced NSCLC previously treated with crizotinib. 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. 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. **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 full leaflet).** [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 (> 5 times ULN) with total bilirubin 2 times ULN→Temporarily withhold until recovery to baseline or Grade 1 (≤ 3 times ULN), then resume at reduced dose (see Table 1)/ ALT or AST elevation of Grade ≥ 2 (> 3 times ULN) with total bilirubin elevation > 2 times ULN in the absence of cholestasis or haemolysis→Permanently discontinue Alecensa/Bradycardia[a] Grade 2 or Grade 3 (symptomatic, may be severe and medically significant, medical intervention indicated) Temporarily withhold until recovery to ≤ Grade 1 (asymptomatic) bradycardia or to a heart rate of ≥ 60 bpm. Evaluate concomitant 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). [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 of SmPC). 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 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 36.9123 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 of SmPC). CONTRAINDICATIONS Hypersensitivity to alectinib or to any of the excipients as listed in 6.1 of SmPC. UNDESIRABLE EFFECTS *Summary of the safety profile.* The data described below reflect exposure to Alecensa in 405 patients with ALK-positive advanced NSCLC who participated in one randomised Phase III clinical trial (BO28984) and in two single-arm phase II clinical trials (NP28761, NP28673). These patients were treated with the recommended dose of 600 mg twice daily. In the phase II clinical trials (NP28761, NP28673; N=253), the median duration of exposure to Alecensa was 11.2 months. In BO28984 (ALEX; N=152) the median duration of exposure to Alecensa was 28.1 months, whereas the median duration of exposure to crizotinib was 10.8 months. The most common adverse drug reactions (ADRs) (≥ 20%) were constipation, myalgia, oedema, anaemia, rash, increased bilirubin and nausea. *Tabulated list of ADRs.* Table 3 lists the ADRs occurring in patients who received Alecensa across two phase II clinical trials (NP28761, NP28673) and one phase III clinical trial (BO28984; ALEX), and during post-marketing. 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 (NP28761, NP28673, BO28984; N=405) and during post-marketing** (System organ class ADRs (MedDRA), Alecensa N=405 Frequency category (all grades), Frequency category (grades 3-4). **Blood and lymphatic system disorders:** Anaemia[1)], Very common, Common. Haemolytic anaemia[2)], Uncommon, -*. **Nervous system disorders:** Dysgeusia[3)], Common, Uncommon. **Eye disorders:** Vision disorders[4)], Very common, -*. **Cardiac disorders:** Bradycardia[5)], Very common, -˙. **Respiratory, thoracic and mediastinal disorders:** Interstitial lung disease/pneumonitis, Common, Uncommon, .**Gastrointestinal disorders:** Constipation, Very common, Uncommon. Nausea, Very common, Uncommon. Diarrhoea, Very common, Common. Vomiting, Very common, Uncommon. Stomatitis [6)], Common, -˙. **Hepatobiliary disorders:** Increased bilirubin [7)], Very common, Common. Increased AST, Very common, Common. Increased ALT, Very common, Common. Increased alkaline phosphatase[8)], Common, Uncommon. Drug-induced liver injury [9)], Uncommon, Uncommon. **Skin and subcutaneous tissue disorders:** Rash [10)], Very common, Common. Photosensitivity, Common, Uncommon. **Musculoskeletal and connective tissues disorders:** Myalgia [11)], Very common, Common. Increased blood creatine phosphokinase, Very common, Common. **Renal and urinary disorders:** Blood creatinine increased, Common, Uncommon**. Acute kidney injury, Common, Common**. **General disorders and administration site conditions:** Oedema [12)], Very common, Common. **Investigations:** Weight increased, Very common, Uncommon. * No grade 3-4 ADRs were observed ** Includes one Grade 5 event. 1) includes cases of anaemia and haemoglobin decreased. 2) Cases of haemolytic anaemia have been reported in the post-marketing period and two cases suggestive of haemolytic anaemia have been reported in clinical trials. The following studies (N=716) have been included in the frequency calculation: NP28761, NP28673, BO28984, MO29750, BO39694, BO29554 cohort A, YO29449. 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) Increased alkaline phosphatase was reported in the post-marketing period and in pivotal phase II and phase III clinical trials. 9) 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. 10) includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic, rash macular and exfoliative rash. 11) includes cases of myalgia, musculoskeletal pain and arthralgia. 12) includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema, face oedema and localised oedemaDescription of selected adverse reactions. The safety profile of Alecensa was generally consistent across the pivotal phase III clinical trial BO28984 (ALEX) and phase II trials (NP28761, NP28673). Interstitial lung disease (ILD) / pneumonitis. Severe ILD/pneumonitis occurred in patients treated with Alecensa. Across clinical trials (NP28761, NP28673, BO28984), 1 out of 405 patients treated with Alecensa (0.2%) had a Grade 3 ILD. This event led to withdrawal from Alecensa treatment. 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 of SmPC). Hepatotoxicity. Across clinical trials (NP28761, NP28673, BO28984) two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. In addition, one patient experienced a Grade 4 adverse event of drug-induced liver injury. Two of these cases led to withdrawal from Alecensa treatment. Adverse reactions of increased AST and ALT levels (17% and 16% respectively) were reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 3.7% and 3.7% 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 1.5% and 3.0% of the patients, respectively) or dose reduction (2.0% and 1.5%, respectively). In 1.2% and 1.5% 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 21% of the patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). The majority of the events were of Grade 1 and 2 intensity; Grade 3 events were reported in 3.7% 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 2.0% 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 of SmPC and managed as recommended in section 4.2 of SmPC. Bradycardia. Cases of bradycardia (11%) of Grade 1 or 2 have been reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). No patients had events of Grade 3 severity. There were 66 of 365 patients (18%) treated with Alecensa who had post-dose heart rate values below 50 beats per minutes (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 (35%) including myalgia events (23%) and musculoskeletal pain (0.5%) and arthralgia (19%) have been reported in patients treated with Alecensa across clinical trials (NP28761, NP28673, BO28984). The majority of events were Grades 1 or 2 and four patients (1.0%) had a Grade 3 event. Dose modifications of Alecensa treatment due to these adverse events were only required for two patients (0.5%); Alecensa treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 48% of 363 patients with CPK laboratory data available across clinical trials (NP28761, NP28673, BO28984) with Alecensa. The incidence of Grade ≥ 3 elevations of CPK was 4.2%. Median time to Grade ≥ 3 CPK elevation was 14 days across trials (NP28761, NP28673, BO28984). Dose modifications for elevation of CPK occurred in 3.5% 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* Cases of haemolytic anaemia have been reported in the post-marketing period, with severity of anaemia ranging from Grade 1 to Grade 3. Out of the 30 events with known outcome and known action taken with alectinib, the majority (66.7%) recovered or were recovering following a dose modification of alectinib; 10.0% recovered without any dose modification. Across the following clinical trials (NP28761, NP28673, BO28984, MO29750, BO39694, BO29554 cohort A, YO29449), 2 out of 716 patients treated with Alecensa (0.3%) experienced non-serious Grade 1 events suggestive of haemolytic anaemia. One of these cases led to interruption of Alecensa treatment. No Grade 4 or Grade 5 (fatal) cases of haemolytic anaemia were observed in the clinical trials or in the post-marketing setting (see sections 4.2 and 4.4). Gastrointestinal effects. Constipation (38%), nausea (20%), diarrhoea (19%) and vomiting (14%) were the most commonly reported gastrointestinal (GI) reactions. Most of these events were of mild or moderate severity; Grade 3 events were reported for diarrhea (1.0%), nausea (0.5%), vomiting (0.2%), and constipation (0.2%). These events did not lead to withdrawal from Alecensa treatment. Median time to onset for constipation, nausea, diarrhea, and/or vomiting events across clinical trials (NP28761, NP28673, BO28984) was 22 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system. *België/Belgique* : Federaal agentschap voor geneesmiddelen en gezondheidsproducten /Agence fédérale des médicaments et des produits de santé - Afdeling Vigilantie / Division Vigilance -Galileelaan 5/03 1210 BRUSSEL / Avenue Galilée 5/03 1210 BRUXELLES or Postbus 97 1000 BRUSSEL Madou / Boîte Postale 97 1000 BRUXELLES Madou - Website: www.eenbijwerkingmelden.be / Site internet: www.notifieruneffetindesirable.be - e-mail: adr@afmps.be- *Luxembourg* : Centre Régional de Pharmacovigilance de Nancy - Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) - CHRU de Nancy – Hôpitaux de Brabois - Rue du Morvan - F-54 511 VANDOEUVRE LES NANCY CEDEX - Tél : (+33) 3 83 65 60 85 / 87 - E-mail : crpv@chru-nancy.fr ou Direction de la Santé – Division de la Pharmacie et des Médicaments, 20, rue de Bitbourg, L-1273 Luxembourg-Hamm, Tél. : (+352) 2478 5592 - E-mail : pharmacovigilance@ms.etat.lu. 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