▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See full leaflet for how to report adverse reactions. 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 treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (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). 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]: Starting 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. [a] Heart rate less than 60 beats per minute (bpm*). Special populations. Hepatic impairment.* No dose adjustment is required in patients with mild hepatic impairment. Alecensa has not been studied in patients with moderate to severe hepatic impairment. Therefore, Alecensa is not recommended in patients with moderate to severe hepatic impairment (see section 5.2 of SmPC). *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 (seesection 5.2 of SmPC). *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 36.9−123 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 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 safety of Alecensa has been evaluated in 253 patients in pivotal phase II clinical trials (NP28761, NP28673) with ALK-positive non-small cell lung cancer (NSCLC) treated with the recommended dose of 600 mg twice daily. The median duration of exposure to Alecensa was 11 months. The most common adverse drug reactions (ADRs) (≥ 20%) were constipation (36%), oedema (34%, including oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema), myalgia (31%, including myalgia and musculoskeletal pain) and nausea (22%). *Tabulated list of ADRs.* Table 3 summarises the ADRs occurring in patients who received Alecensa in pivotal clinical trials. 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 frequency grouping, undesirable effects are presented in order of decreasing seriousness. **Table 3: Summary of ADRs occurring in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673) and during post-marketing.** (System organ class ADRs (MedDRA), Alecensa N=253 All grades (%), Frequency category (all grades), Grades 3-4* (%)). **Blood and lymphatic system disorders:** Anaemia[1)], 16%, Very common, 2.0%. **Eye disorders:** Vision disorders[2)], 12%, Very common, 0%. **Cardiac disorders:** Bradycardia[3)], 7.9%, Common, 0%. **Respiratory, thoracic and mediastinal disorders:** Interstitial lung disease/pneumonitis, 0.4%, Uncommon, 0.4%. **Gastrointestinal disorders:** Diarrhoea, 18%, Very common, 1.2%. Vomiting, 13%, Very common, 0.4%. Constipation, 36%, Very common, 0%. Nausea, 22%, Very common, 0.4%. **Hepatobiliary disorders:** Drug-induced liver injury [4)], 0.8%, Uncommon, 0.8%. Increased aspartate aminotransferase (AST), 16%, Very common, 2.8%. Increased alanine aminotransferase (ALT), 14%, Very common, 3.2%. Increased bilirubin[5)], 17%, Very common, 3.2%. Increased alkaline phosphatase**, 7,5%, Common, 0,4%. **Skin and subcutaneous tissue disorders:** Rash [6)], 20%, Very common, 0.4%. Photosensitivity, 12%, Very common, 0%. **Musculoskeletal and connective tissues disorders:** Myalgia[7)], 31%, Very common, 1.2%. Increased blood creatine phosphokinase, 13%, Very common, 3.6%. **Renal and urinary disorders:** Blood creatinine increased, 6.7%, Common, 0.4%. **General disorders and administration site conditions:** Oedema[8)], 34%, Very common, 0.8%. * No Grade 5 events observed. ** Increased alkaline phosphatase was reported in the post-marketing period. Cases were also reported in pivotal Phase II clinical trials NP28761 and NP28673.[1)] includes cases of anaemia and haemoglobin decreased. [2)] includes cases of blurred vision, visual impairment, vitreous floaters, reduced visual acuity, asthenopia, and diplopia. 3) includes cases of bradycardia and sinus bradycardia. [4)] 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. [5)] includes cases of blood bilirubin increased, hyperbilirubinaemia and bilirubin conjugated increased. [6)] includes cases of rash, rash maculopapular, dermatitis acneiform, erythema, rash generalised, rash papular, rash pruritic and rash macular. [7)] includes cases of myalgia and musculoskeletal pain. [8)] includes cases of oedema peripheral, oedema, generalised oedema, eyelid oedema, periorbital oedema. Description of selected adverse reactions. Interstitial lung disease (ILD) / pneumonitis. Severe ILD/pneumonitis occurred in patients treated with Alecensa. In the pivotal phase II clinical trials (NP28761, NP28673), 1 out of 253 patients treated with Alecensa (0.4%) had a Grade 3 ILD. This event led to withdrawal from Alecensa treatment. There were no fatal cases of ILD. Patients should be monitored for pulmonary symptoms indicative of pneumonitis (see sections 4.2 and 4.4 of SmPC). Hepatotoxicity. In the pivotal phase II clinical trials (NP28761, NP28673) two patients with Grade 3-4 AST/ALT elevations had documented drug induced liver injury by liver biopsy. One of these cases led to withdrawal from Alecensa treatment. Adverse reactions of increased AST and ALT levels (16% and 14% respectively) were reported in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673). The majority of these events were of Grade 1 and 2 intensity, and events of Grade ≥ 3 were reported in 2.8% and 3.2% of the patients, 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 1.2% and 3.2% of the patients, respectively) or dose reduction (1.6% and 0.8%, respectively). In 1.2% and 1.6% of the patients, AST and ALT elevations, respectively, led to withdrawal from Alecensa treatment. Adverse reactions of bilirubin elevations were reported in 17% of the patients treated with Alecensa in pivotal phase II clinical trials (NP28761,

NP28673). The majority of the events were of Grade 1 and 2 intensity; Grade 3 events were reported in 3.2% of the patients. The events generally occurred during the first 3 months of treatment, were usually transient and resolved upon temporary interruption of Alecensa treatment (4.7% of the patients) or dose reduction (2.8%). In 4 patients (1.6%), bilirubin elevations led to withdrawal from Alecensa treatment. 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 and managed as recommended in the full leaflet. Bradycardia. Cases of bradycardia (7.9%) of Grade 1 or 2 have been reported in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673). There were 44 of 221 patients (20%) treated with Alecensa who had post-dose heart rate values below 50 beats per minutes. 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 (31%) including myalgia events (25%) and musculoskeletal pain (7.5%) have been reported in patients treated with Alecensa in pivotal phase II clinical trials (NP28761, NP28673). The majority of events were Grades 1 or 2 and three patients (1.2%) had a Grade 3 event. Dose modifications of Alecensa treatment due to these adverse events were only required for two patients (0.8%); Alecensa treatment was not withdrawn due to these events of myalgia. Elevations of CPK occurred in 46% of 219 patients with CPK laboratory data available in pivotal phase II clinical trials (NP28761, NP28673) with Alecensa. The incidence of Grade 3 elevations of CPK was 5.0%. Median time to Grade 3 CPK elevation was 14 days. Dose modifications for elevation of CPK occurred in 4.0% of patients; withdrawal from Alecensa treatment did not occur due to CPK elevations. Gastrointestinal effects. Constipation (36%), nausea (22%), diarrhoea (18%) and vomiting (13%) 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 (1.2%), nausea (0.4%), and vomiting (0.4%). These events did not lead to withdrawal from Alecensa treatment. Median time to onset for constipation, nausea, diarrhea, and/or vomiting events was 18 days. The events declined in frequency after the first month of treatment. 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 -EUROSTATION II, Place Victor Hortaplein, 40/ 40 - B-1060 Brussel/ Bruxelles - Website: www.fagg.be / Site internet: www.afmps.be - e-mail: adversedrugreactions@fagg-afmps.be - *Luxembourg* : Direction de la Santé – Division de la Pharmacie et des Médicaments, Villa Louvigny – Allée Marconi, L-2120 Luxembourg, Site internet: http://www.ms.public.lu/fr/activites/pharmacie-medicament/index.html MARKETING AUTHORISATION HOLDER Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom MARKETING AUTHORISATION NUMBER EU/1/16/1169/001 MODE OF DELIVERY on medical prescription DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 16/02/2017 DATE OF REVISION OF TEXT 09/06/2017. Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu . R.E. Dr. Chr. Lenaerts - BE/ONCO/0717/0035 – 14/07/2017