ALUNBRIG®
BRIGATINIB

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Zaventem, datum van de post

Betreft: Nieuwe terugbetaling

Takeda Belgium informeert u dat de specialiteit ALUNBRIG® ▼ vanaf 1 september 2021 in België is terugbetaald voor de volgende indicatie:

Gebruik als monotherapie voor de eerstelijnsbehandeling van volwassen patiënten met ALK-positief (anaplastisch-lymfoomkinase) gevorderd niet-kleincellig longcarcinoom (NSCLC) die niet eerder zijn behandeld met een ALK-remmer.

PRIJSLIJST

CODE CNK	AFGIFTE	VERPAKKINGEN	PRIJS BUITEN BEDRIJF (zonder taxen)	VERGOEDINGS-BASIS
7731-458	ZIEKENHUIS	Alunbrig 30 mg, 1X28 tabletten	1.048,59 €	1.048,59 €
7731-433		Alunbrig 90 mg, 1X28 tabletten	3.138,96 €	3.138,96 €
7731-441		Alunbrig 180 mg, 1X28 tabletten	4.918,64 €	4.918,64 €
7731-466		Alunbrig starterpack, 90mg 1X7 tab. + 180mg 1x21 tabletten	4.473,72 €	4.473,72 €

TERUGBETALINGSCRITERIA

Hfdst VIII § 370108 (nieuw, eerste aanvraag)

a) De farmaceutische specialiteit op basis van brigatinib komt voor vergoeding in aanmerking voor de eenmalige beoordelingsperiode van maximum 12 weken indien ze wordt toegediend in monotherapie in het kader van de eerstelijnsbehandeling van een volwassen rechthebbende met ALK-positief gevorderd niet-kleincellig longcarcinoom (NSCLC) die niet eerder is behandeld met een ALK-remmer. ALK-positiviteit moet aangetoond zijn door middel van minstens een van volgende voor longcarcinoom gevalideerde testen: IHC, ISH of NGS (next generation sequencing). De test(en) moeten worden uitgevoerd in laboratoria die de validatie van de analyseprocedures kunnen garanderen.

b) De FISH test of NGS test moet voldoen aan de voorwaarden van artikel 33ter van het koninklijk besluit van 14 september 1984 betreffende moleculairbiologische testen op menselijk materiaal bij verworven aandoeningen die geassocieerd zijn aan een farmaceutische specialiteit.

c) De vergoeding kan enkel worden toegestaan indien de betrokken farmaceutische specialiteit wordt voorgeschreven door een arts-specialist verantwoordelijk voor de behandeling en die erkend is in de medische oncologie of die erkend is in de pneumologie en een bijzondere bekwaamheid in de oncologie heeft.

d) Deze behandeling is slechts vergoed als die, voorafgaand aan de opstart ervan, goedgekeurd werd door het multidisciplinair oncologisch consult (MOC), waarvan het rapport door de arts-specialist vermeld onder punt c) wordt bijgehouden in het dossier.

e) Het aantal vergoedbare verpakkingen gedurende deze beoordelingsperiode zal rekening houden met een posologie-schema met een aanbevolen startdosis van 90 mg eenmaal daags tijdens de eerste 7 dagen en vervolgens 180 mg eenmaal daags.

f) De behandeling wordt niet meer vergoed bij vaststelling van ziekteprogressie volgens de RECIST 1.1 criteria geëvalueerd door radiodiagnostische onderzoeken van de laesies ondanks de lopende behandeling. Met het oog hierop verbindt de arts-specialist vermeld onder punt c) zich ertoe om de rechthebbende te evalueren ten laatste in de loop van de 12e week die volgt op de aanvang van de behandeling en vroeger indien de klinische situatie dit vereist. Bij deze evaluatie zal een CT-scan of een MRI worden uitgevoerd.

g) De vergoeding kan gedurende een eerste periode van maximaal 12 weken worden toegestaan, op basis van een elektronische aanvraag, ingediend door de via het e-Health platform geïdentificeerde en geauthentificeerde arts-specialist vermeld onder punt c) die daardoor verklaart:

- *dat alle voorwaarden in punt a) zijn vervuld ;*
- *dat de tumor ALK positief is;*
- *dat hij/zij er zich toe verbindt om een medisch rapport dat chronologisch de evolutie van de aandoening beschrijft (resultaten van de medische beeldvorming) en de bewijsstukken die de geattesteerde gegevens bevestigen (resultaten van de anatomopathologische onderzoeken en van de predictieve test,…) ter beschikking te houden van de adviserend-arts ;*
- *dat hij/zij in zijn/haar medisch dossier over het rapport van het multidisciplinair oncologisch consult (MOC) beschikt dat het akkoord voor de behandeling waarvoor terugbetaling wordt aangevraagd vermeldt ;*
- *dat hij/zij weet dat voor het aantal vergoedbare verpakkingen rekening wordt gehouden met een posologie schema met een aanbevolen startdosis van 90 mg eenmaal daags tijdens de eerste 7 dagen en vervolgens 180 mg eenmaal daags ;*
- *dat hij/zij zich ertoe verbindt om een klinische evaluatie uit te voeren evenals een beeldvorming door CT-scan of MRI ten laatste in de loop van de 12e week die volgt op de aanvang van de behandeling en vroeger indien de klinische situatie dit vereist ;*
- *dat hij/zij weet dat de behandeling niet meer vergoed wordt bij vaststelling van ziekteprogressie volgens de RECIST 1.1 criteria geëvalueerd door radiodiagnostische onderzoeken van de laesies ondanks de lopende behandeling.*

h) De vergoeding mag alleen toegekend worden als de betrokken ziekenhuisapotheker, vooraleer hij/zij de specialiteit verstrekt, beschikt over een bewijs van de elektronische goedkeuring bedoeld in g).

Hfdst IV § 370208 (nieuw, verlenging)

a) De farmaceutische specialiteit op basis van brigatinib komt voor vergoeding in aanmerking voor hernieuwbare periodes van 1 jaar indien ze wordt toegediend in monotherapie in het kader van de eerstelijnsbehandeling van een volwassen rechthebbende met ALK-positief gevorderd niet-kleincellig longcarcinoom (NSCLC) die niet eerder is behandeld met een ALK-remmer. ALK-positiviteit moet aangetoond zijn door middel van minstens een van volgende voor longcarcinoom gevalideerde testen: IHC, ISH of NGS (next generation sequencing). De test(en) moeten worden uitgevoerd in laboratoria die de validatie van de analyseprocedures kunnen garanderen.

Deze behandeling is slechts terugbetaald als voldaan wordt aan de volgende cumulatieve voorwaarden:

- *De rechthebbende werd reeds behandeld met brigatinib;*
- *De medische beeldvorming gerealiseerd bij de rechthebbende in de loop van de 12e week die volgt op de aanvang van de behandeling zoals bepaald onder punt b) van paragraaf § 370208 van hoofdstuk VIII van dit besluit, geeft geen progressie van de laesies volgens de RECIST 1.1 criteria weer.*

b) De FISH test of NGS test moet voldoen aan de voorwaarden van artikel 33ter van het koninklijk besluit van 14 september 1984 betreffende moleculairbiologische testen op menselijk materiaal bij verworven aandoeningen die geassocieerd zijn aan een farmaceutische specialiteit.

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c) De vergoeding kan enkel worden toegestaan indien de betrokken specialiteit wordt voorgeschreven door een arts-specialist verantwoordelijk voor de behandeling en die erkend is in de medische oncologie of die erkend is in de pneumologie en een bijzondere bekwaamheid in de oncologie heeft.

d) Deze behandeling is slechts vergoed als die, voorafgaand aan de opstart ervan, goedgekeurd werd door het multidisciplinair oncologisch consult (MOC), waarvan het rapport door de arts-specialist vermeld onder punt c) wordt bijgehouden in het dossier.

e) Het aantal vergoedbare verpakkingen zal rekening houden met een posologie-schema met een aanbevolen startdosis van 90 mg eenmaal daags tijdens de eerste 7 dagen en vervolgens 180 mg eenmaal daags.

f) De behandeling wordt niet meer vergoed bij vaststelling van ziekteprogressie volgens de RECIST 1.1 criteria geëvalueerd door radiodiagnostische onderzoeken van de laesies ondanks de lopende behandeling. Met het oog hierop verbindt de arts-specialist vermeld onder punt c) zich ertoe om de rechthebbende te evalueren na elke periode van 12 weken behandeling (of vroeger indien de klinische situatie dit vereist). Bij deze evaluatie zal een CT-scan of een MRI worden uitgevoerd.

g) De vergoeding kan voor hernieuwbare periodes van maximaal 1 jaar worden toegestaan, op basis van een elektronische aanvraag, ingediend door de via het e-Health platform geïdentificeerde en geauthentificeerde arts-specialist vermeld onder punt c) die daardoor verklaart:

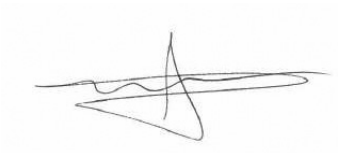
- *dat alle voorwaarden in punt a) zijn vervuld ;*
- *dat de tumor ALK positief is ;*
- *dat hij/zij er zich toe verbindt om een medisch rapport dat chronologisch de evolutie van de aandoening beschrijft (resultaten van de medische beeldvorming) en de bewijsstukken die de geattesteerde gegevens bevestigen (resultaten van de anatomopathologische onderzoeken en van de predictieve test,…) ter beschikking te houden van de adviserend-arts ;*
- *dat hij/zij weet dat voor het aantal vergoedbare verpakkingen rekening wordt gehouden met een posologie schema met een aanbevolen startdosis van 90 mg eenmaal daags tijdens de eerste 7 dagen en vervolgens 180 mg eenmaal daags ;*
- *dat hij/zij er zich toe verbindt om een klinische evaluatie uit te voeren evenals een beeldvorming door CT-scan of MRI elke 12 weken en vroeger indien de klinische situatie dit vereist ;*
- *dat hij/zij weet dat de behandeling niet meer vergoed wordt bij vaststelling van ziekteprogressie volgens de RECIST 1.1 criteria geëvalueerd door radiodiagnostische onderzoeken van de laesies ondanks de lopende behandeling.*

h) De vergoeding mag alleen toegekend worden als de betrokken ziekenhuisapotheker, vooraleer hij/zij de specialiteit verstrekt, beschikt over een bewijs van de elektronische goedkeuring bedoeld in g).

Voor meer informatie over het product
kunt u contact opnemen met onze Key Account Manager Sabine Vanlerberghe per e-mail via Sabine.Vanlerberghe@takeda.com of telefonisch op + 32/478-23-67-43.

Wij danken u voor uw vertrouwen,

Met vriendelijke groeten



T'JAMPENS, Davy
Head of Patient Value & Access

Seynhaeve, Vincent
Head of Medical and Regulatory Affairs

▼ This medicine 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 section Undesirable effects for how to report adverse reactions. **NAME OF THE MEDICINAL PRODUCT** Alunbrig 30 mg film coated tablets Alunbrig 90 mg film coated tablets Alunbrig 180 mg film coated tablets **QUALITATIVE AND QUANTITATIVE COMPOSITION** Alunbrig 30 mg film coated tablets. Each film coated tablet contains 30 mg of brigatinib. Excipient with known effect Each film coated tablet contains 56 mg of lactose monohydrate. Alunbrig 90 mg film coated tablets Each film coated tablet contains 90 mg of brigatinib. Excipient with known effect. Each film coated tablet contains 168 mg of lactose monohydrate. Alunbrig 180 mg film coated tablets. Each film coated tablet contains 180 mg of brigatinib.Excipient with known effect. Each film coated tablet contains 336 mg of lactose monohydrate.**PHARMACEUTICAL FORM.** Film coated tablet (tablet). Alunbrig 30 mg film coated tablets.Round, white to off white film coated tablet of approximately 7 mm in diameter with debossed "U3" on one side and plain on the other side. Alunbrig 90 mg film coated tablets. Oval, white to off white film coated tablet of approximately 15 mm in length with debossed "U7" on one side and plain on the other side. Alunbrig 180 mg film coated tablets. Oval, white to off white film coated tablet of approximately 19 mm in length with debossed "U13" on one side and plain on the other side.**THERAPEUTIC INDICATIONS**. Alunbrig is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor. Alunbrig is indicated as monotherapy for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib. **POSOLOGY AND METHOD OF ADMINISTRATION.** Treatment with Alunbrig should be initiated and supervised by a physician experienced in the use of anticancer medicinal products. ALK positive NSCLC status should be known prior to initiation of Alunbrig therapy. A validated ALK assay is necessary for the selection of ALK positive NSCLC patients. Assessment for ALK positive NSCLC should be performed by laboratories with demonstrated proficiency in the specific technology being utilised. Posology The recommended starting dose of Alunbrig is 90 mg once daily for the first 7 days, then 180 mg once daily. If Alunbrig is interrupted for 14 days or longer for reasons other than adverse reactions, treatment should be resumed at 90 mg once daily for 7 days before increasing to the previously tolerated dose.If a dose is missed or vomiting occurs after taking a dose, an additional dose should not be administered and the next dose should be taken at the scheduled time. Treatment should continue as long as clinical benefit is observed. Dose adjustments Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. Alunbrig dose reduction levels are summarised in Table 1. **Table 1: Recommended Alunbrig dose reduction levels**. **Dose:** 90 mg once daily. (first 7 days). **Dose reduction levels**. **First:** reduce to 60 mg once daily. **Second:** permanently discontinue **Third**: not applicable. **Dose:** 180 mg once daily. **Dose reduction levels**. **First:** reduce to 120 mg once daily. **Second:** reduce to 90 mg once daily. **Third**: reduce to 60 mg once daily. Alunbrig should be permanently discontinued if patient is unable to tolerate the 60 mg once daily dose. Recommendations for dose modifications of Alunbrig for the management of adverse reactions are summarised in Table 2. **Table 2: Recommended Alunbrig dose modifications for adverse reactions. Adverse reaction. Severity*. Dose modification** Interstitial lung disease (ILD)/pneumonitis. Grade 1. If event occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level and not escalated to 180 mg once daily. If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at same dose level. If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued. Grade 2. If ILD/pneumonitis occurs during the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline, then resumed at next lower dose level as described in Table 1 and not escalated to 180 mg once daily. If ILD/pneumonitis occurs after the first 7 days of treatment, Alunbrig should be withheld until recovery to baseline. Alunbrig should be resumed at next lower dose level as described in Table 1. If ILD/pneumonitis recurs, Alunbrig should be permanently discontinued. Grade 3 or 4. Alunbrig should be permanently discontinued. Hypertension. Grade 3 hypertension. (SBP ≥ 160 mmHg or DBP ≥ 100 mmHg, medical intervention indicated, more than one anti hypertensive medicinal product, or more intensive therapy than previously used indicated). Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at same dose. If Grade 3 hypertension recurs, Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 then resumed at the next lower dose level per Table 1 or permanently discontinued. Grade 4 hypertension (life threatening consequences, urgent intervention indicated) Alunbrig should be withheld until hypertension has recovered to Grade ≤ 1 (SBP < 140 mmHg and DBP < 90 mmHg), then resumed at the next lower dose level per Table 1 or permanently discontinued. If Grade 4 hypertension recurs, Alunbrig should be permanently discontinued. Bradycardia (Heart Rate less than 60 bpm). Symptomatic bradycardia. Alunbrig should be withheld until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. If a concomitant medicinal product known to cause bradycardia is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at same dose upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. If no concomitant medicinal product known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose modified, Alunbrig should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. Bradycardia with life threatening consequences, urgent intervention indicated. If contributing concomitant medicinal product is identified and discontinued, or its dose is adjusted, Alunbrig should be resumed at the next lower dose level per Table 1 upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. Alunbrig should be permanently discontinued if no contributing concomitant medicinal product is identified. Alunbrig should be permanently discontinued in case of recurrence. Elevation of CPK. Grade 3 or 4 elevation of CPK (> 5.0 × ULN) with Grade ≥ 2 muscle pain or weakness. Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) elevation of CPK or to baseline, then resumed at the same dose. If Grade 3 or 4 elevation of CPK recurs with Grade ≥ 2 muscle pain or weakness, Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 2.5 × ULN) elevation of CPK or to baseline, then resumed at the next lower dose level per Table 1.Elevation of lipase or amylase. Grade 3 elevation of lipase or amylase (> 2.0 × ULN).Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resumed at same dose. If Grade 3 elevation of lipase or amylase recurs, Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN) or to baseline, then resumed at the next lower dose level per Table 1. Grade 4 elevation of lipase or amylase (> 5.0 x ULN). Alunbrig should be withheld until recovery to Grade ≤ 1 (≤ 1.5 × ULN), then resumed at the next lower dose level per Table 1. Hepatotoxicity. Grade ≥ 3 elevation (> 5.0 × ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with bilirubin 2 × ULN. Alunbrig should be withheld until recovery to baseline or less than or equal to 3 × ULN, then resumed at next lower dose per Table 1. Grade ≥ 2 elevation (> 3 × ULN) of ALT or AST with concurrent total bilirubin elevation > 2 × ULN in the absence of cholestasis or haemolysis.Alunbrig should be permanently discontinued. Hyperglycaemia. For Grade 3 (greater than 250 mg/dL or 13.9 mmol/L) or greater. If adequate hyperglycaemic control cannot be achieved with optimal medical management, Alunbrig should be withheld until adequate hyperglycaemic control is achieved. Upon recovery, Alunbrig may either be resumed at the next lower dose per Table 1 or permanently discontinued. Visual Disturbance. Grade 2 or 3. Alunbrig should be withheld until recovery to Grade 1 or baseline, then resumed at the next lower dose level per Table 1. Grade 4. Alunbrig should be permanently discontinued. Other adverse reactions. Grade 3. Alunbrig should be withheld until recovery to baseline, then resumed at the same dose level. If the Grade 3 event recurs, Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued. Grade 4. Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1. If the Grade 4 event recurs, Alunbrig should be withheld until recovery to baseline, then resumed at the next lower dose level as per Table 1 or permanently discontinued. bpm = beats per minute; CPK = Creatine Phosphokinase; DBP = diastolic blood pressure; SBP = systolic blood pressure; ULN = upper limit of normal. *Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4). *Special populations*. *Elderly patients*. The limited data on the safety and efficacy of Alunbrig in patients aged 65 years and older suggest that a dose adjustment is not required in elderly patients (see section Undesirable effects). There are no available data on patients over 85 years of age. *Hepatic impairment*. No dose adjustment of Alunbrig is required for patients with mild hepatic impairment (Child Pugh class A) or moderate hepatic impairment (Child Pugh class B). A reduced starting dose of 60 mg once daily for the first 7 days, then 120 mg once daily is recommended for patients with severe hepatic impairment (Child Pugh class C). *Renal impairment*. No dose adjustment of Alunbrig is required for patients with mild or moderate renal impairment (estimated glomerular filtration rate (eGFR) ≥ 30 mL/min). A reduced starting dose of 60 mg once daily for the first 7 days, then 90 mg once daily is recommended for patients with severe renal impairment (eGFR < 30 mL/min) (see section 5.2). Patients with severe renal impairment should be closely monitored for new or worsening respiratory symptoms that may indicate ILD/pneumonitis (e.g., dyspnoea, cough, etc.) particularly in the first week. *Paediatric population*. The safety and efficacy of Alunbrig in patients less than 18 years of age have not been established. No data are available. Method of administration. Alunbrig is for oral use. The tablets should be swallowed whole and with water. Alunbrig may be taken with or without food. Grapefruit or grapefruit juice may increase plasma concentrations of brigatinib and should be avoided. **CONTRAINDICATIONS**. Hypersensitivity to the active substance or to any of the excipients. **UNDESIRABLE EFFECTS**. Summary of the safety profile.The most common adverse reactions (≥ 25%) reported in patients treated with Alunbrig at the recommended dosing regimen were increased AST, increased CPK, hyperglycaemia, increased lipase, hyperinsulinaemia, diarrhoea, increased ALT, increased amylase, anaemia, nausea, fatigue, hypophosphataemia, decreased lymphocyte count, cough, increased alkaline phosphatase, rash, increased APTT, myalgia, headache, hypertension, decreased white blood cell count, dyspnoea, and vomiting. The most common serious adverse reactions (≥ 2%) reported in patients treated with Alunbrig at the recommended dosing regimen other than events related to neoplasm progression were pneumonia, pneumonitis, dyspnoea and pyrexia. Tabulated list of adverse reactions The data described below reflect exposure to Alunbrig at the recommended dosing regimen in three clinical trials: a Phase 3 trial (ALTA 1L) in patients with advanced ALK positive NSCLC previously not treated with an ALK inhibitor (N = 136), a Phase 2 trial (ALTA) in patients treated with Alunbrig with ALK positive NSCLC who previously progressed on crizotinib (N = 110), and a phase 1/2 dose escalation/expansion trial in patients with advanced malignancies (N = 28). Across these studies, the median duration of exposure in patients receiving Alunbrig at the recommended dosing regimen was 21.8 months. Adverse reactions reported are presented in Table 3 and are listed by system organ class, preferred term and frequency. Frequency categories are very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of frequency. **Table 3: Adverse reactions reported in patients treated with Alunbrig (per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03) at the 180 mg regimen (N = 274). System organ class. Frequency. category. Adverse reactions† all grades. Adverse reactions Grade 3 4.** Infections and infestations. Very common (all grades): Pneumonia[a,b] Upper respiratory tract infection. Common (grade 3-4): Pneumonia[a]. Blood and lymphatic system disorders. Very common (all grades): Anaemia. Lymphocyte count decreased. APTT increased. White blood cell count decreased. Neutrophil count decreased. Very common (grade 3-4): Lymphocyte count decreased. Common (all grades): Decreased platelet count. Common (grade 3-4): APTT increased. Anaemia. Uncommon (grade 3-4): Neutrophil count decreased. Metabolism and nutrition disorders. Very common (all grades): Hyperglycaemia. Hyperinsulinaemiac. Hypophosphataemia. Hypomagnesaemia. Hypercalcaemia. Hyponatraemia. Hypokalaemia. Decreased appetite. Common (grade 3-4): Hypophosphataemia. Hyperglycaemia. Hyponatraemia. Hypokalaemia. Decreased appetite. Psychiatric disorders. Common (all grades): Insomnia. Nervous system disorders. Very common (all grades): Headache[d]. Peripheral neuropathye. Dizziness. Common (all grades): Memory impairment. Dysgeusia. (grade 3-4): Headache[d]. Peripheral neuropathye. Uncommon (grade 3-4): Dizziness. Eye disorders. Very common (all grades): Visual disturbance. Common (grade 3-4): Visual disturbance[f]. Cardiac disorders. Common (all grades): Bradycardia[g]. Electrocardiogram QT prolonged. Tachycardia[h]. Palpitations. (grade 3-4): Electrocardiogram QT prolonged. Uncommon (grade 3-4): Bradycardia[g]. Vascular disorders. Very common (all grades): Hypertension[i]. (grade 3-4): Hypertension[i]. Respiratory, thoracic and mediastinal disorders. Very common (all grades): Cough. Dyspnoea[j]. Common (all grades): Pneumonitis[k]. (grade 3-4): Pneumonitis[k]. Dyspnoea[j]. Gastrointestinal disorders. Very common (all grades): Lipase increased. Diarrhoea. Amylase increased. Nausea. Vomiting. Abdominal pain[l]. Constipation. Stomatitism. (grade 3-4): Lipase increased. Common (all grades): Dry mouth. Dyspepsia. Flatulence. (grade 3-4): Amylase increased. Nausea. Abdominal pain[l]. Diarrhoea. Uncommon (all grades): Pancreatitis. (grade 3-4) Vomiting. Stomatitism. Dyspepsia. Pancreatitis. Hepatobiliary disorders. Very common (all grades): AST increased. ALT increased. Alkaline phosphatase increased. Common (all grades): Blood lactate dehydrogenase increased. Hyperbilirubinaemia. (grade 3-4): ALT increased. AST increased. Alkaline phosphatase increased. Uncommon (grade 3-4): Hyperbilirubinaemia. Skin and subcutaneous tissue disorders. Very common (all grades): Rash. Pruritus[o]. Common (all grades): Dry skin. Photosensitivity reaction. (grade 3-4): Rash[n]. Photosensitivity reaction. Uncommon (grade 3-4): Dry skin. Pruritus[o]. Musculoskeletal and connective tissue disorders. Very common (all grades): Blood CPK increased. Myalgia[p]. Arthralgia. (grade 3-4): Blood CPK increased. Commom (all grades): Musculoskeletal chest pain. Pain in extremity. Musculoskeletal stiffness. Uncommon (grade 3-4): Pain in extremity. Musculoskeletal chest pain. Myalgia[p]. Renal and urinary disorders. Very commom (all grades): Blood creatinine increased. General disorders and administration site conditions. Very common (all grades): Fatigue[q]. Oedemar. Pyrexia. Common (all grades): Non cardiac chest pain; Chest discomfort. Pain. (grade 3-4): Fatigue[q]. Uncommon (grade 3-4): Pyrexia. Oedemar. Non cardiac chest pain. Investigations. Common (all grades): Blood cholesterol increased[s]. Weight decreased. Uncommon (grade 3-4): Weight decreased. † The frequencies for ADR terms associated with chemistry and haematology laboratory changes were determined based on the frequency of abnormal laboratory shifts from baseline.. [a] Includes atypical pneumonia, pneumonia, pneumonia aspiration, pneumonia cryptococcal, lower respiratory tract infection, lower respiratory tract infection viral, lung infection. [b] Includes Grade 5 events. [c] Grade not applicable. [d] Includes headache, sinus headache, head discomfort, migraine, tension headache. [e] Includes paraesthesia, peripheral sensory neuropathy, dysaesthesia, hyperaesthesia, hypoaesthesia, neuralgia, neuropathy peripheral, neurotoxicity, peripheral motor neuropathy, polyneuropathy, burning sensation, post herpetic neuralgia. [f] Includes altered visual depth perception, cataract, colour blindness acquired, diplopia, glaucoma, intraocular pressure increased, macular oedema, photophobia, photopsia, retinal oedema, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous detachment, vitreous floaters, amaurosis fugax. [g] Includes bradycardia, sinus bradycardia. [h] Includes sinus tachycardia, tachycardia, atrial tachycardia, heart rate increased. [i] Includes blood pressure increased, diastolic hypertension, hypertension, systolic hypertension.[j] Includes dyspnoea, dyspnoea exertional. [k] Includes interstitial lung disease, pneumonitis. [l] Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort. [m] Includes aphthous stomatitis, stomatitis, aphthous ulcer, mouth ulceration, oral mucosal blistering. [n] Includes dermatitis acneiform, erythema, exfoliative rash, rash, rash erythematous, rash macular, rash maculo papular, rash papular, rash pruritic, rash pustular, dermatitis, dermatitis allergic, dermatitis contact, generalised erythema, rash follicular, urticaria, drug eruption, toxic skin eruption. [o] Includes pruritus, pruritus allergic, pruritus generalised, pruritus genital, vulvovaginal pruritus. [p] Includes musculoskeletal pain, myalgia, muscle spasms, muscle tightness, muscle twitching, musculoskeletal discomfort. [q] Includes asthenia, fatigue. [r] Includes eyelid oedema, face oedema, oedema peripheral, periorbital oedema, swelling face, generalised oedema, peripheral swelling, angioedema, lip swelling, periorbital swelling, skin swelling, swelling of eyelid. [s] Includes blood cholesterol increased, hypercholesterolemia. Description of selected adverse reactions. *Pulmonary adverse reactions.*In ALTA 1L, 2.9% of patients experienced any Grade ILD/pneumonitis early in treatment (within 8 days), with Grade 3 4 ILD/pneumonitis in 2.2% of patients. There were no fatal ILD/pneumonitis. Additionally, 3.7% of patients experienced pneumonitis later in treatment. In ALTA, 6.4% of patients experienced pulmonary adverse reactions of any grade, including ILD/pneumonitis, pneumonia and dyspnoea, early in treatment (within 9 days, median onset: 2 days); 2.7% of patients had Grade 3 4 pulmonary adverse reactions and 1 patient (0.5%) had fatal pneumonia. Following Grade 1 2 pulmonary adverse reactions, treatment with Alunbrig was either interrupted and then restarted or the dose was reduced. Early pulmonary adverse reactions also occurred in a dose escalation study in patients (N = 137) (Study 101) including three fatal cases (hypoxia, acute respiratory distress syndrome and pneumonia). Additionally, 2.3% of patients in ALTA experienced pneumonitis later in treatment, with 2 patients having Grade 3 pneumonitis. *Elderly*. Early pulmonary adverse reaction was reported in 10.1% of patients ≥ 65 years of age compared with 3.1% of patients < 65 years of age. *Hypertension.* Hypertension was reported in 30% of patients treated with Alunbrig at the 180 mg regimen with 11% having Grade 3 hypertension. Dose reduction for hypertension occurred in 1.5% at the 180 mg regimen. Mean systolic and diastolic blood pressure, in all patients, increased over time . *Bradycardia*. Bradycardia was reported in 8.4% of patients treated with Alunbrig at the 180 mg regimen. Heart rates of less than 50 beats per minute (bpm) were reported in 8.4% of patients at the 180 mg regimen. *Visual disturbance*. Visual disturbance adverse reactions were reported in 14% of patients treated with Alunbrig at the 180 mg regimen. Of these, three Grade 3 adverse reactions (1.1%) including macular oedema and cataract were reported. Dose reduction for visual disturbance occurred in two patients (0.7%) at the 180 mg regimen. *Peripheral neuropathy*. Peripheral neuropathy adverse reactions were reported in 20% of patients treated at the 180 mg regimen. Thirty-three percent of patients had resolution of all peripheral neuropathy adverse reactions. The median duration of peripheral neuropathy adverse reactions was 6.6 months, with a maximum duration of 28.9 months. *Creatine phosphokinase (CPK) elevation;* In ALTA 1L and ALTA, elevations of CPK were reported in 64% of patients treated with Alunbrig at the 180 mg regimen. The incidence of Grade 3 4 elevations of CPK was 18%. The median time to onset for CPK elevations was 28 days. Dose reduction for CPK elevation occurred in 10% of patients at the 180 mg regimen. *Elevations of pancreatic enzymes.* Elevations of amylase and lipase were reported in 47% and 54% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for amylase and lipase were 7.7% and 15%, respectively. The median time to onset for amylase elevations and lipase elevations was 17 days and 29 days, respectively. Dose reduction for elevation of lipase and amylase occurred in 4.7% and 2.9% of patients, respectively at the 180 mg regimen.*Elevation of hepatic enzymes*. Elevations of ALT and AST were reported in 49% and 68% of patients treated with Alunbrig, respectively at the 180 mg regimen. For elevations to Grade 3 and 4, the incidences for ALT and AST were 4.7% and 3.6%, respectively. Dose reduction for elevation of ALT and AST occurred in 0.7% and 1.1% of patients, respectively at the 180 mg regimen. *Hyperglycaemia.* Sixty one percent of patients experienced hyperglycaemia. Grade 3 hyperglycemia occurred in 6.6% of patients.No patients had dose reductions due to hyperglycaemia. 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: **Belgium**. Agence fédérale des médicaments et des produits de santé. Division Vigilance EUROSTATION II Place Victor Horta, 40/ 40 B-1060 Bruxelles Site internet : www.afmps.be. e-mail : adversedrugreactions@fagg-afmps.be **Luxemburg. Centre Régional de Pharmacovigilance de Nancy** Bâtiment de Biologie Moléculaire et de Biopathologie (BBB). CHRU de Nancy – Hôpitaux de Brabois. Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX. Tél. : (+33) 3 83 65 60 85 / 87. Fax : (+33) 3 83 65 61 33. E-mail : crpv@chru-nancy.fr or **Direction de la Santé Division de la Pharmacie et des Médicaments.** Allée Marconi – Villa Louvigny. L-2120 Luxembourg. Tél. : (+352) 2478 5592. Fax : (+352) 2479 5615. E-mail : pharmacovigilance@ms.etat.lu. Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html. **NATURE AND CONTENTS OF CONTAINER.** Alunbrig 30 mg film coated tablets. Round wide mouth high density polyethylene (HDPE) bottles with two piece polypropylene child resistant screw cap closures with foil induction seal liner, containing either 60 or 120 film coated tablets, together with one HDPE canister containing a molecular sieve desiccant. Clear thermoformable poly chloro tri fluoro ethylene (PCTFE) blister with heat sealable paper laminated foil lidding in a carton, containing either 28, 56 or 112 film coated tablets. Alunbrig 90 mg film coated tablets. Round wide mouth high density polyethylene (HDPE) bottles with two piece polypropylene child resistant screw cap with foil induction seal liner closures, containing either 7 or 30 film coated tablets, together with one HDPE canister containing a molecular sieve desiccant. Clear thermoformable poly chloro tri fluoro ethylene (PCTFE) blister with heat sealable paper laminated foil lidding in a carton, containing either 7 or 28 film coated tablets. Alunbrig 180 mg film coated tablets. Round wide mouth high density polyethylene (HDPE) bottles with two piece polypropylene child resistant screw cap with foil induction seal liner closures, containing 30 film coated tablets, together with one HDPE canister containing a molecular sieve desiccant. Clear thermoformable poly chloro tri fluoro ethylene (PCTFE) blister with heat sealable paper laminated foil lidding in a carton, containing 28 film coated tablets. Treatment initiation pack Alunbrig 90 mg and 180 mg film coated tablets. Each pack consists of an outer carton with two inner cartons containing: Alunbrig 90 mg film coated tablets. 1 clear thermoformable poly chloro tri fluoro ethylene (PCTFE) blister with heat sealable paper laminated foil lidding in a carton, containing 7 film coated tablets. Alunbrig 180 mg film coated tablets. 3 clear thermoformable poly chloro tri fluoro ethylene (PCTFE) blisters with heat sealable paper laminated foil lidding in a carton, containing 21 film coated tablets. Not all pack sizes may be marketed. **MARKETING AUTHORISATION HOLDER.** Takeda Pharma A/S. Delta Park 45. 2665 Vallensbaek Strand.Denmark. **MARKETING AUTHORISATION NUMBER(S)**. Alunbrig 30 mg film coated tablets. EU/1/18/1264/001. 60 tablets in bottle.EU/1/18/1264/002. 20 tablets in bottle. EU/1/18/1264/011. 28 tablets in carton. EU/1/18/1264/003. 56 tablets in carton. EU/1/18/1264/004. 112 tablets in carton. Alunbrig 90 mg film coated tablets. EU/1/18/1264/007. 7 tablets in bottle. EU/1/18/1264/006. 30 tablets in bottle. EU/1/18/1264/007. 7 tablets in carton. EU/1/18/1264/008. 28 tablets in carton. Alunbrig 180 mg film coated tablets. EU/1/18/1264/009. 30 tablets in bottle. EU/1/18/1264/010. 28 tablets in carton. Alunbrig treatment initiation pack. EU/1/18/1264/012. 7 x 90 mg + 21 x 180 mg tablets in carton. **LEGAL STATUS**. Medicinal product subject to medical prescription. **DATE OF REVISION OF THE TEXT** 08/2020. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

C-APROM/BE/ALUN/0018 – SEPT 2021