アレセンサカプセル150 mg
に関する資料

当該資料に記載された情報に係る権利及び内容についての責任は，中外製薬株式会社に帰属するものであり，当該情報を適正使用以外の営利目的に利用することはできません。

中外製薬株式会社

アレセンサカプセル 150 mg
（アレクチニブ塩酸塩）

[*ALK* 融合遺伝子陽性の非小細胞肺癌における術後補助療法]

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.5 起原又は発見の経緯及び開発の経緯

中外製薬株式会社

目次

1.5　起原又は発見の経緯及び開発の経緯 2

1.5　起原又は発見の経緯及び開発の経緯

アレクチニブ塩酸塩は，中外製薬株式会社で創製された未分化リンパ腫キナーゼ（ALK）阻害剤であり，ALK を選択的に阻害することにより，腫瘍細胞の増殖を阻害し，アポトーシスを誘導することで，抗腫瘍効果を示すと考えられている。本邦では，アレクチニブとして150 mg を含有した製剤（販売名「アレセンサ®カプセル150 mg」，以下，本剤）が，「*ALK* 融合遺伝子陽性の切除不能な進行・再発の非小細胞肺癌」及び「再発又は難治性の *ALK* 融合遺伝子陽性の未分化大細胞リンパ腫」の効能・効果で承認されている。

Union Internationale Contre le Cancer（UICC）/American Joint Committee on Cancer（AJCC）第7版に従い，IB（腫瘍径4 cm 以上）～IIIA 期の *ALK* 融合遺伝子陽性の非小細胞肺癌（NSCLC）完全切除例を対象に術後補助療法として，本剤とプラチナ製剤併用化学療法の有効性及び安全性を比較する BO40336試験の結果から，本剤が IB～IIIA 期の *ALK* 融合遺伝子陽性の NSCLC 完全切除例を対象とした術後補助療法として高い臨床的有用性を有すると考えられたことから，「*ALK* 融合遺伝子陽性の非小細胞肺癌における術後補助療法」を本剤の効能・効果に追加する医薬品製造販売承認事項一部変更承認申請を行うこととした。

臨床に関する概括評価については2.5項に，また非臨床試験の概括評価については2.4項に記載した。開発の経緯図を図 1.5-1　開発の経緯図に示す。

図 1.5-1　開発の経緯図

試験項目		国内	海外	試験内容	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
非臨床	毒性		○	反復投与試験	④				⑪						
臨床	第III相		○	BO40336試験											



図中の算用数字は当該試験の開始月を示す。

アレセンサカプセル 150 mg
（アレクチニブ塩酸塩）

[*ALK* 融合遺伝子陽性の非小細胞肺癌における術後補助療法]

第1部　（モジュール1）：

申請書等行政情報及び添付文書に関する情報

1.6 外国における使用状況等に関する資料

中外製薬株式会社

目次

1.6 外国における使用状況等に関する資料 2
1.6.1 外国における承認申請状況 2
1.6.2 代表的な外国添付文書の和訳概要 3
1.6.2.1 米国添付文書の和訳概要 3
1.6.2.2 欧州添付文書の和訳概要 17
1.6.3 米国における添付文書 28
1.6.4 欧州における添付文書 56
1.6.5 企業中核データシート(Core Data Sheet) 104

1.6　外国における使用状況等に関する資料

1.6.1　外国における承認申請状況

アレセンサカプセル150mg（以下，本剤）の外国における承認申請状況を以下に記載する。

「クリゾチニブに不応又は不耐容の *ALK* 陽性の転移性非小細胞肺癌」の効能・効果に対して2015年12月に米国で迅速承認を，2017年2月に欧州連合（EU：European Union）で条件付き承認を取得し，103の国又は地域で承認を取得している。

また，「*ALK* 陽性の進行非小細胞肺癌へのアレセンサ単剤での一次治療」については，米国，EU でそれぞれ，2017年11月，2017年12月に承認を取得し，100の国又は地域で承認を取得している。

「*ALK* 融合遺伝子陽性の非小細胞肺癌における術後補助療法」については，2023年11月に米国及び欧州で申請を行った。2024年7月1日時点で，2024年4月に米国で承認を取得し、2024年6月に欧州で European Commission による承認を取得した。。

本剤の代表的な外国添付文書として，米国添付文書及び欧州添付文書の和訳概要を1.6.2に，米国添付文書の原文，欧州添付文書の原文及び本剤の企業中核データシート（Core Data Sheet）をそれぞれ1.6.3，1.6.4，1.6.5に添付する。

1.6.2　代表的な外国添付文書の和訳概要

1.6.2.1　米国添付文書の和訳概要

本剤の代表的な外国添付文書として，米国の添付文書(2024年4月版)の和訳概要を以下に示す。

販売名

ALECENSA® (Alectinib) capsules

1　効能・効果

アレセンサは，FDA が承認した検査により検出された未分化リンパ腫キナーゼ(ALK)陽性非小細胞肺癌（NSCLC）（4 cm 以上の腫瘍又はリンパ節陽性）の腫瘍切除後の成人患者における補助療法を適応とする*［用法・用量（2.1）参照］*。

アレセンサは，FDA が承認した検査により検出された未分化リンパ腫キナーゼ(ALK)陽性転移性非小細胞肺癌(NSCLC)患者の治療を適応とする。

2　用法・用量

2.1　患者の選択

腫瘍組織における ALK 陽性の存在に基づいて，アレセンサによる NSCLC の術後補助療法の対象患者選択すること*［効能・効果（1.1）及び臨床試験（14.1）参照］*。

腫瘍組織又は血漿試料における ALK 陽性の存在に基づいて，アレセンサによる転移性 NSCLC の治療対象患者を選択すること*［「効能・効果（1）」及び「臨床試験（14）」を参照］*。血漿試料で ALK 遺伝子再構成が検出されない場合，可能であれば腫瘍組織を検査すること。

NSCLC における ALK 遺伝子再構成を検出するための FDA が承認した検査については，http://www.fda.gov/CompanionDiagnostics を参照。

2.2　用法・用量

- アレセンサの推奨用量は 600 mg1 日 2 回経口投与である*［臨床薬理(12.3)参照］*。投与は，病勢進行に至るまで，又は許容できない毒性が発現するまで行う。術後補助療法における投与は，合計 2 年間又は再発もしくは許容できない毒性が認められるまでとする。
- 重度肝機能障害(Child-Pugh C)患者に対する推奨用量は，450 mg 1 日 2 回経口投与である。*［特別な集団への投与(8.7)及び臨床薬理(12.3)を参照］*
- アレセンサは食事とともに服用すること。カプセルを開封したりカプセル内容物を溶解したりしてはならない。服用を忘れたり，服用後に嘔吐した場合，次回投与分は予定された時刻に服用すること。

2.3　副作用に対する用量調節

重度の肝障害（Child-Pugh C）を有する患者におけるアレセンサの推奨用量は、450mg を1日2回経口投与である*［特定集団における使用（8.7）および臨床薬理（12.3）を参照］*。

- アレセンサの減量スケジュールを表 1 に示す。

表1:アレセンサの減量スケジュール

減量スケジュール	用量レベル
開始用量	600 mg を1日2回経口投与
1回目の減量	450 mg を1日2回経口投与

2回目の減量	300 mg を1日2回経口投与

患者が300 mg 1日2回投与に耐えられない場合は，投与を中止する。

- 副作用が発現した場合のアレセンサの推奨用量変更方法を表 2 に示す。

表2:副作用に対するアレセンサの用量調節

基準[a]	アレセンサの用量変更
ALT 又は AST の基準値上限(ULN)の5倍を超える増加，かつ総ビリルビン≦2×ULN	ベースライン又は3×ULN 以下に回復するまで休薬し，その後は表1に従い減量した用量で投与を再開する。
ALT 又は AST の3×ULN を超える増加，かつ総ビリルビンの2×ULN を超える増加であって，胆汁うっ滞や溶血がみられない	投与を永続的に中止する。
総ビリルビンの3×ULN を超える増加	ベースライン又は1.5×ULN 以下に回復するまで休薬し，その後は表1に従い減量した用量で投与を再開する。
投与に関連した間質性肺疾患(ILD)/肺臓炎(Grade にかかわらない)	投与を永続的に中止する。
Grade 3の腎機能障害	血清クレアチニン値が1.5×ULN 以下に回復するまで休薬し，その後は減量した用量で投与を再開する。
Grade 4の腎機能障害	投与を永続的に中止する。
症候性徐脈	無症候性徐脈又は心拍数60拍/分以上に回復するまで休薬する。 徐脈の一因となる併用薬が特定され投与を中止した場合，又はその用量を調節した場合は，無症候性徐脈又は心拍数60拍/分以上に回復した時点で，アレセンサの投与を同用量で再開する。 徐脈の一因となる併用薬が特定されない場合，又は徐脈の一因となる併用薬の投与中止や用量変更を行わない場合は，無症候性徐脈又は心拍数60拍/分以上に回復した時点で，アレセンサの投与を減量した用量(表1参照)で再開する。
徐脈[b](生命を脅かす転帰，緊急の介入が必要)	徐脈の一因となる併用薬が特定されない場合，アレセンサの投与を永続的に中止する。 徐脈の一因となる併用薬が特定され投与を中止した場合，又はその用量を調節した場合は，無症候性徐脈又は心拍数60拍/分以上に回復した時点で，アレセンサの投与を減量した用量(表1参照)で再開し，臨床的必要性に応じて頻回のモニタリングを行う。再発した場合はアレセンサの投与を永続的に中止する。

5×ULN を超える CPK 増加	ベースライン又は2.5×ULN 以下に回復するまで休薬し，その後は同用量で投与を再開する。
10×ULN を超える CPK 増加，又は5×ULN を超える CPK 増加の再発	ベースライン又は2.5×ULN 以下に回復するまで休薬し，その後は表1に従い減量した用量で投与を再開する。
溶血性貧欠血	溶血性貧血が疑われる場合は，アレセンサを休薬する。溶血性貧血が回復した時点で，減量して再開するか，恒久的に中止する。

[a] ALT＝ アラニントランスアミナーゼ，AST＝ アスパラギン酸トランスアミナーゼ，ULN＝ 基準値上限，ILD＝ 間質性肺疾患，CPK＝ 血中クレアチンホスホキナーゼ
[b] 心拍数60拍/分(bpm)未満

3　剤形・含量
150 mg硬カプセル剤，白色，キャップに黒インクで「ALE」，ボディーに黒インクで「150 mg」と印字。

4　禁忌
なし。

5　警告及び使用上の注意
5.1　肝毒性
アレセンサの投与を受けた患者において、薬物性肝障害を含む重度の肝毒性が発現した。アレセンサの投与を受けた患者の併合安全性解析対象集団*［副作用（6.1項）参照］*では、肝毒性は41%の患者に認められ、Grade 3以上の肝毒性は8%であった。ALINA 試験では、アレセンサの投与を受けた患者の61%に肝毒性が発現した。Grade 3以上の肝毒性は4.7%であった。トランスアミナーゼ上昇の大部分（136例中72%）は投与開始後3ヵ月以内に発現した。肝毒性による投与中止は、併合安全性解析対象集団でアレセンサの投与を受けた患者の3.6%、ALINA 試験で投与を受けた患者の1.6%で認められた。
臨床試験でアレセンサが投与された患者の1%未満において，ALT 又は AST の3×ULN 以上の増加と総ビリルビンの2×ULN 以上の増加が同時にみられたが，アルカリホスファターゼは正常値であった。Grade 3～4の AST/ALT 増加がみられた患者3例が，薬物性肝障害であった(2例は肝生検により確認)。肝機能検査(ALT，AST 及び総ビリルビンを含む)を，投与開始後最初の3カ月間は2週間に1回，以後は月1回及び臨床的必要性に応じて行い，トランスアミナーゼとビリルビンの増加があらわれた患者ではより頻回に検査を行うこと。この副作用の重症度に基づき，表2記載の通りアレセンサを休薬し，減量した用量で投与を再開するか，又は投与を永続的に中止すること*[用法・用量(2.3)を参照]*

5.2　間質性肺疾患(ILD)/肺臓炎
アレセンサの投与を受けた患者に ILD が発現した。
併合安全性解析対象集団*［副作用（6.1項）参照］*では、アレセンサ投与患者の1.3%に ILD/肺臓炎が発現し、0.4%に Grade 3の ILD/肺臓炎が発現した。
併合安全性解析対象集団の5例（0.9%）が ILD/肺臓炎のためにアレセンサの投与を中止した。Grade 3以上の ILD/肺臓炎の発現までの期間の中央値は2.1ヵ月（範囲:0.6ヵ月~3.6ヵ月）であった。ILD/肺臓炎と診断された患者ではアレセンサを直ちに休薬し，ILD/肺臓炎の他の原因の可能性が特定されなかった場合は，アレセンサの投与を永続的に中止する。*[用法・用量(2.3)及び副作用*

(6)を参照]。

5.3　　腎機能障害

アレセンサの投与を受けた患者において、死亡例を含む腎機能障害が認められた。
併合安全性解析対象集団では*［副作用（6.1項）を参照］*、アレセンサの投与を受けた患者の12%に腎機能障害が発現し、1.7%に Grade 3以上の事象が認められ、そのうち0.4%は致死的な事象であった。Grade 3以上の腎機能障害が発現するまでの期間の中央値は3.7ヵ月（範囲:0.5~31.8ヵ月）であった。腎機能障害により患者の2.4%で用量変更が必要となった。
Grade 4の腎毒性があらわれた場合，アレセンサの投与を永続的に中止する。Grade 3の腎毒性の場合は1.5×ULN 以下に回復するまでアレセンサを休薬し，その後は減量した用量で投与を再開する。*[用法・用量(2.3)を参照]*

5.4　　徐脈

アレセンサの投与を受けた患者で症候性徐脈が認められた。
併合安全性解析対象集団では*［副作用（6.1項）を参照］*、アレセンサの投与を受けた患者の11%に徐脈が認められた。アレセンサの投与を受け、連続心電図（ECG）が得られた患者521例の20%で、投与後の心拍数が50回/分（bpm）未満であった。
心拍数と血圧を定期的にモニタリングすること。無症候性徐脈の場合，用量変更の必要はない。生命を脅かすものでない症候性徐脈の場合，無症候性徐脈又は心拍数60拍/分以上に回復するまでアレセンサを休薬し，徐脈をもたらすことが知られている併用薬と高血圧治療薬を調べる。徐脈が併用薬によるものであると判断された場合，無症候性徐脈又は心拍数60拍/分以上に回復した時点で，アレセンサの投与を減量した用量(表1参照)で再開し，臨床的必要性に応じて頻回にモニタリングを行う。再発した場合はアレセンサの投与を永続的に中止する。生命を脅かす徐脈であって，徐脈の一因となる併用薬が特定されない場合は，アレセンサの投与を永続的に中止する。*[用法・用量(2.3)を参照]*

5.5　　重度の筋肉痛及びクレアチンホスホキナーゼ(CPK)増加

アレセンサの投与を受けた患者に重度の筋肉痛及び CPK 増加が発現した。
併合安全性解析対象集団*［副作用（6.1項）参照］*では、筋肉痛（筋肉及び筋骨格系に関連する反応を含む）がアレセンサの投与を受けた患者の31%に発現し、0.8%が Grade 3以上であった。筋肉痛事象により患者の2.1%で用量変更が必要となった。
併合安全性解析対象集団では、 CPK の臨床検査データが得られた491例のうち、 アレセンサの投与を受けた患者の56%に CPK 増加が発現し、Grade 3以上は6%であった。Grade 3以上の CPK 増加が発現するまでの期間の中央値は15日（四分位範囲:-15‑337日）であった。CPK 増加による用量変更は患者の5%で行われた。
ALINA 試験では、CPK 検査データが得られた患者128例の77%に CPK 増加が認められ、Grade 3以上の増加は6%であった。
患者に対して，原因不明の筋肉痛，圧痛又は脱力があらわれた場合は報告するよう指導すること。CPK 値を，投与開始後最初の1カ月間は2週間に1回，及び症状が報告された患者では臨床的必要性に応じて評価すること。CPK 増加の重症度に基づき，アレセンサを休薬し，その後投与を再開するか，又は用量を減量する。*[用法・用量(2.3)を参照]*

5.6　　溶血性貧血

アレセンサの投与を受けた患者に溶血性貧血が発現した。
アレセンサでは、市販後において、直接抗グロブリン試験（DAT）陰性の症例を含む溶血性貧血が最初に報告された。その後、ALINA 試験で溶血性貧血の判定のための評価を収集したところ、アレセンサの投与を受けた患者の3.1%で溶血性貧血が認められた。

溶血性貧血が疑われる場合は，アレセンサを休薬し，適切な臨床検査を開始すること。溶血性貧血が確定した場合，回復した時点で減量して再開するか，アレセンサの恒久的な中止を検討すること*［「用法・用量（2.3）」を参照］*。

5.7　胚・胎児毒性

動物実験の知見及び作用機序から，アレセンサを妊婦に投与すると胎児に有害となる可能性がある。アレクチニブを器官形成期の妊娠ラット及び妊娠ウサギに投与したとき，母体毒性があらわれる用量(アレクチニブ600 mg を1日2回投与したヒトにおける曝露量の約2.7倍)において，胚・胎児毒性及び流産に至った。妊婦に対して，胎児に対する危険性を説明すること。妊娠可能な女性に対して，アレセンサ投与中及び最終投与後1週間にわたり，有効な避妊法を使用するよう指導すること。*[特別な集団における使用(8.1及び8.3)及び臨床薬理(12.1)を参照]*

6　副作用

以下の臨床的に重大な副作用についての詳細は他項を参照のこと。

- 肝毒性*［警告及び使用上の注意(5.1)参照］*
- 間質性肺疾患(ILD)/肺臓炎*［警告及び使用上の注意(5.2)参照］*
- 腎機能障害*［警告及び使用上の注意(5.3)参照］*
- 徐脈*［警告及び使用上の注意(5.4)参照］*
- 重度の筋肉痛及びクレアチンホスホキナーゼ(CPK)増加*［警告及び使用上の注意(5.5)参照］*
- 溶血性貧血*［警告及び使用上の注意(5.6)参照］*
- 胚・胎児毒性警告及び使用上の注意*［警告及び使用上の注意(5.7)参照］*

6.1　臨床試験成績

臨床試験はさまざまな条件で行われるため，ある薬剤の臨床試験でみられた副作用発現率を別の薬剤の臨床試験における発現率と直接比較することはできない。また，臨床試験でみられた副作用発現率が実際の臨床においてみられる副作用発現率を反映するとも限らない。

ALK 陽性 NSCLC に対する術後補助療法

ALINA 試験（切除後の ALK 陽性 NSCLC 患者の補助療法としての多施設共同、非盲検、無作為化試験）において、アレセンサの安全性を評価した*［臨床成績（14.1項）参照］*。DFS の解析時、曝露期間の中央値はアレセンサ群で23.9ヵ月、プラチナ製剤ベースの化学療法群で2.1ヵ月であった。

アレセンサの投与を受けた患者の13%に重篤な副作用が発現した。最も高頻度に認められた重篤な副作用（1%超）は、肺炎（3.9%）、虫垂炎（3.1%）、及び急性心筋梗塞（1.6%）であった。

患者の5%が有害事象により ALECENSA の投与を永続的に中止した;投与中止に至った主な副作用（1%超）は肺臓炎及び肝毒性であった。

患者の27%が副作用により ALECENSA の投与を中断した。2%を超える患者で投与中断を要した副作用は、肝毒性、血中 CPK 増加、COVID-19、筋肉痛、腹痛及び肺炎であった。

副作用により ALECENSA を減量した患者は26%であった。2%を超える患者で減量を要した副作用は、肝毒性、血中 CPK 増加、発疹、徐脈及び筋肉痛であった。

ALINA 試験で認められた主な副作用及び臨床検査値異常を表3及び表4に要約する。

表3:ALINA 試験でアレセンサの投与を受けた患者に発現した副作用（10%超）

副作用	**アレセンサ 128例**		**化学療法120例**	
	All Grade(%)	Grade 3–4(%)	All Grade(%)	Grade 3–4(%)

肝胆道系障害				
肝毒性 [a]	61	4.7*	13	0
胃腸障害				
便秘	42	0.8*	25	0.8*
腹痛 [b]	13	0	10	1.7*
下痢 [c]	13	0.8*	9	1.7*
筋骨格				
筋肉痛 [d]	34	0.8*	1.7	0
感染症及び寄生虫症				
COVID-19	29	0	0.8	0
一般・全身障害及び投与部位の状態				
疲労 [e]	25	0.8*	28	4.2*
浮腫 [f]	16	0	1.7	0
皮膚及び皮下組織障害				
発疹 [g]	23	1.6*	10	0
呼吸器系障害				
咳 [h]	20	0.8*	3.3	0
呼吸困難 [i]	13	0.8*	2.5	0
腎臓				
腎機能障害	16	0.8*	9	0
神経系障害				
味覚異常[k]	13	0	3.3	0
頭痛	11	0	7	0
臨床検査				
体重増加	13	0.8*	0.8	0
心臓障害				
徐脈[l]	12	0	0	0

NCI CTCAE 第5.0版に基づく

* いずれの事象も Grade 3である。

a アラニンアミノトランスフェラーゼ増加、アスパラギン酸アミノトランスフェラーゼ増加、胆汁酸増加、抱合ビリルビン増加、血中ビリルビン増加、非抱合血中ビリルビン増加、γ-グルタミルトランスフェラーゼ増加、肝毒性、高ビリルビン血症、肝機能検査値上昇、黄疸眼、トランスアミナーゼ上昇を含む。

b 腹部不快感、腹痛、下腹部痛、上腹部痛、腹部圧痛、心窩部不快感、消化器痛を含む。

c 大腸炎及び下痢を含む。

d 筋肉疲労、筋力低下、筋骨格系胸痛、筋骨格硬直、筋肉痛を含む。

e 無力症及び疲労を含む。

f 浮腫、顔面浮腫、限局性浮腫、末梢性浮腫、顔面腫脹及び末梢性腫脹を含む。

g ざ瘡様皮膚炎、水疱性皮膚炎、薬疹、湿疹、発疹、紅斑性皮疹、斑状丘疹状皮疹、丘疹性皮疹、脂漏性皮膚炎、蕁麻疹、乾皮症を含む。

h 咳嗽及び湿性咳嗽を含む。

i 呼吸困難及び労作時呼吸困難を含む。

j 高窒素血症、血中クレアチニン増加、腎クレアチニン・クリアランス減少、糸球体濾過率減少、高クレアチニン血症、腎機能障害、腎不全を含む。

k 味覚異常、味覚障害を含む。

l 徐脈及び洞性徐脈を含む。

ALINA 試験でアレセンサの投与を受けた患者の10%未満に発現した臨床的に重要な副作用:悪心（8%）、嘔吐（7%）、視覚障害（4.7%;霧視、視力低下、光視症を含む）、口内炎（4.7%;口内炎及び口腔内潰瘍形成を含む）、光線過敏性反応（3.9%）及び肺臓炎（2.3%）。

表4:ALINA 試験でアレセンサを投与した患者の20%超に発現した臨床検査値のベースラインからの悪化

パラメータ	**アレセンサ 128例**		**化学療法 120例**	
	All Grade(%)	Grade 3–4(%)	All Grade(%)	Grade 3–4(%)
生化学検査				
CPK 増加	77	8	8	1.7*
AST 増加	75	0.8*	25	0
ビリルビン増加	68	2.3*	4.2	0
アルカリホスファターゼ増加	64	0	14	0
ALT 増加	57	2.3*	28	0
クレアチニン増加	41	0	23	0
尿酸値上昇	30	0	19	0
血液学検査				
ヘモグロビン減少	69	0	67	0.8*

NCI CTCAE 第5.0版に基づく

*すべての事象がグレード

未治療の ALK 陽性転移性 NSCLC

ALEX 試験において，ALK 陽性NSCLC 患者152例を対象としてアレセンサの安全性を評価した。アレセンサへの曝露期間中央値は17.9カ月であった。ALEX 試験集団（n=303）の患者特性は，年齢中央値56歳，年齢65歳未満（77%），女性（56%），白人（50%），アジア人（46%），腺

癌組織型（92%），喫煙歴なし（63%），ECOG PS 0又は1（93%）であった。
重篤な有害事象がアレセンサを投与した患者の28%で発現し，2%以上で報告された重篤な有害事象は肺炎（4.6%）及び腎機能障害（3.9%）であった。Grade 3以上の有害事象はアレセンサ投与群の患者の41%で報告された。致死的な有害事象がアレセンサを投与した患者の3.3%で発現し，腎機能障害（2例），突然死，心停止，肺炎（各1例）であった。11%の患者で副作用によってアレセンサの投与が恒久的に中止された。1%以上の患者でアレセンサの投与中止に至った副作用は，腎機能障害（2.0%），高ビリルビン血症（1.3%），ALT 増加（1.3%），AST 増加（1.3%）であった。有害反応によるアレセンサの投与中断は20%の患者で発生した。2%以上の患者で投与中断を必要とした副作用は ALT 上昇、肺炎などであった。有害反応によるアレセンサの減量は患者の17%に認められました。2%以上の患者で減量を必要とした副作用は、高ビリルビン血症、AST 上昇、ALT 上昇などであった。
表 5及び表 6に，ALEX試験で最も認められた副作用及び臨床検査値異常を示す。

表5: ALEX試験のアレセンサ投与群の患者で発現した副作用（NCI CTCAE全Gradeで10%を超えるもの，又はGrade 3～4で2%以上のもの）

副作用	アレセンサ 152例		クリゾチニブ 151例	
	All Grade(%)	Grade 3–4(%)	All Grade(%)	Grade 3–4(%)
消化器				
便秘	34	0	33	0
悪心	14	0.7	48	3.3
下痢	12	0	45	2.0
全般				
疲労	26	1.3	23	0.7
浮腫 [b]	22	0.7	34	0.7
筋骨格系				
筋肉痛 [c]	23	0	4.0	0
皮膚				
発疹 [d]	15	0.7	13	0
心臓				
徐脈 [e]	11	0	15	0
腎臓				
腎機能障害 [f]	12	3.9*	0	0

NCI CTCAE = NCI による有害事象共通用語規準；MedDRA = ICH 国際医薬用語集；SOC = 器官別大分類。
[a] 疲労及び無力症を含む。
[b] 末梢性浮腫，浮腫，眼瞼浮腫，限局性浮腫，顔面浮腫を含む。
[c] 筋肉痛及び筋骨格痛を含む。
[d] 発疹，斑状丘疹状皮疹，ざ瘡様皮膚炎，紅斑，全身性皮疹，斑状皮疹，丘疹性皮疹，剥脱性皮疹及びそう痒性皮疹を含む。
[e] 徐脈及び洞性徐脈の報告例を含むが，連続 ECG 評価に基づくものではない。
[f] 血中クレアチニン増加，クレアチニン腎クリアランス減少，糸球体濾過率減少及び急性腎障害を含む。
* Grade 5の有害事象2件を含む。

その他の臨床的に重要な副作用として，アレセンサの投与を受けた患者に体重増加(9.9%)，光線過敏性反応(5.3%)，口内炎(3.3%)，間質性肺疾患(1.3%)及び薬物性肝障害(1.3%)が認められた。

表6：ALEX 試験に登録された患者の10%以上に認められた治験薬投与後に発現した臨床検査値の悪化

パラメータ	アレセンサ 152例		クリゾチニブ 151例	
	全Grade(%)	Grade3–4(%)	全Grade(%)	Grade3–4(%)
生化学検査				
高ビリルビン血症[a]	54	5	4.7	0
AST 上昇[b]	50	6	56	11
アルカリホスファターゼ増加[c]	50	0	44	0
ALT 上昇[c]	40	6	62	16
クレアチニンの増加[c, d]	38	4.1	23	0.7
CPK 上昇[e]	37	2.8	52	1.4
低カルシウム血症[a]	29	0	61	1.4
高血糖[f]	22	2.2	19	2.3
低ナトリウム血症[g]	18	6	20	4.1
低カリウム血症[c]	17	2	12	0.7
低アルブミン血症[h]	14	0	57	3.4
高カリウム血症[c]	12	1.4	16	1.4
低リン酸血症[i]	9	1.4	25	2.7
γ-グルタミルトランスフェラーゼの増加[j]	7	0.7	39	4.1
血液学的検査				
貧血[c]	62	7	36	0.7
リンパ球減少症[a]	14	1.4	34	4.1
好中球減少症[c]	14	0	36	7

注：NCI による有害事象共通用語規準 v4.03に基づく。米国国立がん研究所有害事象共通用語規準 v 4.03に基づく。ベースライン後の臨床検査評価がない患者は除外した。

[a] アレクチニブ群147例(うち1例はベースライン値が欠測)，クリゾチニブ群148例

[b] アレクチニブ群147例(うち2例はベースライン値が欠測)，クリゾチニブ群148例

[c] アレクチニブ群147例，クリゾチニブ群148例

[d] ULN の定義に基づきクレアチニンが増加している患者

[e] アレクチニブ群143例(このうち14例でベースライン値が欠測)，クリゾチニブ群143例(このうち13例でベースライン値が欠測)

[f] アレクチニブ群134例(うち18例でベースライン値が欠測)，クリゾチニブ群131例(うち8例でベースライン値が欠測)

[g] アレクチニブ群147例，クリゾチニブ148例(うち1例はベースライン値が欠測)

[h] アレクチニブ群146例(うち1例はベースライン値が欠測)，クリゾチニブ148例(うち1例はベースライン値が欠測)

[I] アレクチニブ群145例(うち2例はベースライン値が欠測)，クリゾチニブ群148例(うち4例はベースライン値が欠測)

[j] アレクチニブ群143例(うち4例はベースライン値が欠測)，148例(うち5例はベースライン値が欠測)。

クリゾチニブによる治療歴のある ALK 陽性転移性 NSCLC

2つの臨床試験（NP28761試験及び NP28673試験）において，アレセンサの投与を受けた ALK 陽性非小細胞肺癌（NSCLC）患者253例を対象に，アレセンサの安全性を評価した。アレセンサへの曝露期間の中央値は9.3カ月であった。169例（67%）が6カ月超，100例（40%）が1年超アレセンサに曝露された。集団特性は，年齢中央値53歳，年齢65歳未満（86%），女性（55%），白人（74%），アジア人（18%），NSCLC 腺癌組織型（96%），喫煙歴なし又は喫煙歴あり（98%），ECOG Performance Status（PS）0又は1（91%），化学療法歴あり（78%）であった。
重篤な副作用が患者の19%に発現した。最も多く報告された重篤な副作用は肺塞栓症（1.2%），呼吸困難（1.2%），高ビリルビン血症（1.2%）であった。致死的な副作用が患者の2.8%に発現し，出血（0.8%），腸管穿孔（0.4%），呼吸困難（0.4%），肺塞栓症（0.4%），心内膜炎（0.4%）であった。6%の患者で副作用によってアレセンサの投与が恒久的に中止された。恒久的な投与中止に至った副作用で最も多くみられたものは，高ビリルビン血症（1.6%），ALT 値増加（1.6%），AST 値増加（1.2%）であった。全体では，推奨用量で治療を開始した患者の23%に1回以上の減量が必要となった。初回減量までの期間の中央値は48日であった。減量又は休薬に至った副作用で最も多くみられたものは，ビリルビン増加（6%），CPK 増加（4.3%），ALT 増加（4.0%），AST 増加（2.8%）及び嘔吐（2.8%）であった。
表 7及び表 8に，NP28761試験及び NP28673試験で多く認められた副作用及び臨床検査値異常を示す。

表7：NP28761試験及び NP28673試験の患者の10%以上（全 Grade）又は2%以上（Grade 3～4）で発現した副作用

副作用	アレセンサ 253例	
	All Grade（%）	Grade3–4（%）*
疲労 [a]	41	1.2
便秘	34	0
浮腫 [b]	30	0.8
筋肉痛 [c]	29	1.2
咳嗽	19	0
発疹 [d]	18	0.4
悪心	18	0
頭痛	17	0.8
下痢	16	1.2
呼吸困難	16	3.6 [e]
背部痛	12	0
嘔吐	12	0.4
体重増加	11	0.4
視覚障害 [f]	10	0

* 有害事象共通用語規準（CTCAE）第4.0版に基づく
[a] 疲労及び無力症を含む
[b] 末梢性浮腫，浮腫，全身性浮腫，眼瞼浮腫，眼窩周囲浮腫を含む
[c] 筋肉痛及び筋骨格痛を含む
[d] 発疹，斑状丘疹状皮疹，ざ瘡様皮膚炎，紅斑，全身性皮疹，丘疹性皮疹，そう痒性皮疹及び斑状皮疹を含む
[e] Grade5の事象を1件含む
[f] 霧視，硝子体浮遊物，視力障害，視力低下，眼精疲労及び複視を含む

NP28761試験及び NP28673試験ではさらに，臨床的に重要な副作用として，アレセンサに曝露された患者の9.9%で光線過敏症が発現した。患者には日光への曝露を避け，広域スペクトル対応の日焼け止めを使用するよう指導した。Grade 2の光線過敏症の発現率は0.4%であり，残りの事象の重症度は Grade 1であった。

表8：NP28761試験及び NP28673試験の患者の20%超で治療により発現した臨床検査値の悪化

パラメータ	アレセンサ N=250	
	全 Grade (%)	Grade 3～4 (%)*
血液生化学検査		
AST 増加	51	3.6
アルカリホスファターゼ増加	47	1.2
CPK 増加 [a]	43	4.6
高ビリルビン血症	39	2.4
高血糖 [b]	36	2.0
ALT 増加	34	4.8
低カルシウム血症	32	0.4
低カリウム血症	29	4.0
クレアチニン増加 [c]	28	0
低リン血症	21	2.8
低ナトリウム血症	20	2.0
血液学的検査		
貧血	56	2.0
リンパ球減少症 [d]	22	4.6

* CTCAE v4.0に基づく。

[a] CPK については n=218（これらの患者のうち91例でベースライン値が欠測）。

[b] 空腹時血糖値については n=152（これらの患者のうち5例でベースライン値が欠測）。

[c] ULN の定義に基づいてクレアチニンが増加した患者のみ。

[d] 白血球については n=217（これらの患者のうち5例でベースライン値が欠測）。

8　特別な集団への投与

8.1　妊娠

リスクの要約

アレセンサは動物試験結果及び作用機序に基づき，妊婦に投与したときに胎児に悪影響を及ぼすおそれがある*［臨床薬理(12.1)参照］*。妊婦に対するアレセンサの投与についてのデータは得られていない。

妊娠ラット及びウサギの器官形成期にアレクチニブを強制経口投与したところ，胚・胎児毒性及び流産が母体毒性用量で認められ，その曝露量はヒトにアレクチニブ600 mg1日2回を投与したときの曝露量の約2.7倍であった*(データ参照)*。妊婦には胎児への潜在的リスクについて説明すること。米国の一般人口において，臨床的に認知されている妊娠における著明な先天障害と流産の背景リスクは，それぞれ2～4%及び15～20%と推定される。

データ

動物データ

ウサギを対象とした胚・胎児予備試験では，器官形成期にアレクチニブを強制経口投与したところ，妊娠ウサギ6匹中3匹で母体毒性量27 mg/kg/日（アレクチニブ 600 mg を1日2回投与したヒトの推定曲線下面積［$AUC_{0\text{-}24h,ss}$］の約2.9倍）で流産又は胚・胎児の完全な死亡に至った。この投与群の残り3匹の妊娠ウサギでは，胎児がほとんど生きておらず，胎児及び胎盤の重量が減少しており，食道後方に鎖骨下動脈があった。ラットの胚・胎児発生予備試験では，器官形成期にア

レクチニブを投与したところ，27 mg/kg/日ですべての妊娠ラットが出生児を完全に喪失した（アレクチニブ 600 mg を1日2回投与したヒトの推定 $AUC_{0\text{-}24h,ss}$ の約4.5倍）。9 mg/kg/日以上の用量（アレクチニブ 600 mg を1日2回投与したヒトの推定 $AUC_{0\text{-}24h,ss}$ の約2.7倍）では，母体毒性の他，胎児体重減少，尿管拡張，胸腺拡張，小さい心室及び薄い心室壁，仙椎数及び尾椎数の減少などの発生毒性が認められた。

8.2　授乳婦

リスクの要約

ヒト母乳中のアレクチニブ又はその代謝物の存在，授乳中の乳児に対するアレクチニブの影響又は泌乳への影響については，知見が得られていない。授乳中の乳児でアレクチニブの重篤な副作用が発現する可能性があるため，授乳中の女性には投与中及び最終投与後1週間は授乳しないよう指導すること。

8.3　生殖能を有する者

アレセンサは、妊婦に投与されると胎児に害を及ぼす可能性があります*［特定集団における使用（8.1）を参照］*。

妊娠検査

アレセンサの投与を開始する前に、生殖可能な女性の妊娠状態を確認してください*［特定集団における使用（8.1）を参照］*。

避妊

女性

妊婦に投与すると胎児に悪影響を及ぼすおそれがある。妊娠可能な女性には，アレセンサの投与中及び最終投与後1週間は有効な避妊法を使用するよう指導すること*［特別な集団への投与(8.1)参照］*。

男性

遺伝毒性所見に基づき，パートナーが妊娠可能な女性である男性には，アレセンサの投与期間中及び最終投与後3ヵ月間は有効な避妊法を用いるよう指導すること*［非臨床毒性(13.1)参照］*。

8.4　小児等への投与

小児患者におけるアレセンサの安全性及び有効性は確立されていない。

動物データ

アレクチニブを用いた幼若動物試験は実施していない。一般毒性試験では，ヒトにアレクチニブ 600 mg を1日2回投与したときの曝露量の約4.5倍以上の曝露量となる用量のアレクチニブをラットに投与したところ，成長中の歯及び骨に変化が認められた。歯の所見は，エナメル芽細胞と象牙芽細胞層の組織病理学的配列異常と共に，変色と歯の大きさの変化を含んだ。また，海綿骨の減少及び大腿骨及び胸骨の破骨細胞活性の増加が認められた。

8.5　高齢者への投与

NP28761、NP28673、ALEX および ALINA で調査された533人の患者のうち19%が65歳以上であった（3.2%が75歳以上）。年齢による有効性の全体的な差は観察されなかった。探索的解析によると、65歳以上の患者では65歳未満の患者に比べて重篤な有害事象の発現率が高く（38%対25%）、

治療中止に至る有害事象の頻度が高く（18%対6%）、用量の変更が多い（48%対35%）ことが示唆された。

8.6　　腎機能障害

軽度又は中等度の腎機能障害患者に対する用量調節は推奨されない。重度の腎機能障害(クレアチニンクリアランスが30 mL/min 未満)又は末期腎疾患を有する患者におけるアレセンサの安全性については検討されていない*［臨床薬理(12.3)参照］*。

8.7　　肝機能障害

軽度(Child-Pugh 分類 A)又は中等度(Child-Pugh 分類 B)の肝機能障害を有する患者に対する用量調節は推奨されない。重度の肝機能障害(Child-Pugh 分類 C)を有する患者では，アレクチニブの曝露量の増加が認められた。重度の肝機能障害(Child-Pugh 分類 C)を有する患者に対するアレセンサの推奨用量は450 mg1日2回経口投与である*［用法・用量(2.2)及び臨床薬理(12.3)参照］*。

1.6.2.2　欧州添付文書の和訳概要

本剤の代表的な外国添付文書として，欧州の添付文書(2024年6月版)の和訳概要を以下に示す。

1　販売名

Alecensa 150 mg hard capsules

3　剤形

硬カプセル剤。長さ19.2 mm の白色の硬カプセル剤で，キャップには黒字で「ALE」，ボディには黒字で「150 mg」と印字されている。

4　臨床関連事項

4.1　効能・効果

- アレセンサ単剤療法は、再発リスクが高い ALK 陽性 NSCLC 成人患者に対する完全腫瘍切除後の補助療法を適応とする（選択基準については 5.1 項を参照）。

- アレセンサ単独療法は，未分化リンパ腫キナーゼ(ALK)陽性進行非小細胞肺癌(NSCLC)の成人患者に対する 1 次治療を適応とする。

- アレセンサ単独療法は，クリゾチニブによる治療歴のある ALK 陽性進行 NSCLC の成人患者に対する治療を適応とする。

4.2　用法・用量

アレセンサによる治療は，抗がん剤の使用経験のある医師が開始し，監督すること。ALK陽性NSCLC患者の選択にはバリデートされたALK測定法が必要である。アレセンサによる治療を開始する前にALK陽性NSCLCの状態を確認すること。

- 用量

アレセンサの推奨用量としては，600 mg(150 mg カプセル4カプセル)を1日2回，食事とともに投与する(総1日量1200 mg)。

重度肝機能障害患者(Child-Pugh C)に対しては，開始用量として450 mg を1日2回，食事とともに投与する(総1日量900 mg)。

- 投与期間

切除したNSCLCに対する術後補助療法

アレセンサの投与は、再発又は許容できない毒性が認められるまで、あるいは 2 年間継続する。

進行NSCLCの治療

アレセンサの投与は，病勢進行に至るまで，又は許容できない毒性が発現するまで継続すること。

- 投与が遅れた場合又は投与を忘れた場合

予定したアレセンサ投与を忘れた場合，忘れた分は，次回投与時刻が6時間以内でない限り服用できる。忘れた分を埋め合わせるため同時に2回分を服用しないこと。アレセンサ服用後に嘔吐した場合，次回投与分は予定された時刻に服用すること。

- 用量調節

有害事象に対処するため，アレセンサの用量減量，休薬又は投与中止を要することがある。アレセンサの用量減量は，忍容性に基づき150 mg 1日2回ずつ行う。患者が300 mg 1日2回投与に耐えられない場合は，アレセンサ投与を永続的に中止すること。

用量変更方法を下の表1及び2に示す。

表1　用量減量スケジュール

用量減量スケジュール	用量
用量	600 mg 1日2回
1回目の用量減量	450 mg 1日2回
2回目の用量減量	300 mg 1日2回

表2　所定の副作用に対する用量変更方法(4.4及び4.8を参照)

CTCAE Grade	アレセンサ投与
ILD/肺臓炎(重症度の Grade にかかわらない)	ILD/肺臓炎の他の原因の可能性が特定されていない限り，投与を直ちにかつ永続的に中止する。
Grade 3以上(＞5×ULN)の ALT 又は AST 増加，かつ総ビリルビン≦2×ULN	ベースライン又は Grade 1以下(3×ULN 以下)に回復するまで休薬し，その後は用量を減量して投与を再開する(表1を参照)。
Grade 2以上(＞3×ULN)の ALT 又は AST 増加，かつ総ビリルビン＞2×ULN であって，胆汁うっ滞や溶血がみられない	投与を永続的に中止する。
Grade 2又は Grade 3の徐脈 [a](症候性，重度かつ医学的に著明であり医学的介入が必要となることがある)	Grade 1以下(無症候性)の徐脈又は心拍数60拍/分以上に回復するまで休薬する。徐脈をもたらすことが知られている併用薬及び高血圧治療薬について調べる。 徐脈の一因となる併用薬が特定され投与を中止した場合，又はその用量を調節した場合は，Grade 1以下(無症候性)の徐脈又は心拍数60拍/分以上に回復した時点で，投与を同用量で再開する。 徐脈の一因となる併用薬が特定されない場合，又は徐脈の一因となる併用薬の投与中止や用量変更を行わない場合は，Grade 1以下(無症候性)の徐脈又は心拍数60拍/分以上に回復した時点で，減量した用量(表1参照)で投与を再開する。
Grade 4の徐脈 [a] (生命を脅かす転帰，緊急の介入が必要)	徐脈の一因となる併用薬が特定されない場合，投与を永続的に中止する。 徐脈の一因となる併用薬が特定され投与を中止した場合，又はその用量を調節した場合は，Grade 1以下(無症候性)の徐脈又は心拍数60拍/分以上に回復した時点で減量した用量(表1参照)で投与を再開し，臨床的必要性に応じて頻回のモニタリングを行う。 再発した場合は投与を永続的に中止する。

5×ULN を超える CPK 増加	ベースライン又は2.5×ULN 以下に回復するまで休薬し，その後は同用量で投与を再開する。
10×ULN を超える CPK 増加，又は5×ULN を超える CPK 増加の再発	ベースライン又は2.5×ULN 以下に回復するまで休薬し，その後は表1に従い減量した用量で投与を再開する。
ヘモグロビン10 g/dL 未満の溶血性貧血(Grade 2以上)	回復するまで休薬し，その後減量して投与を再開する(表1参照)。

ALT = アラニンアミノトランスフェラーゼ，AST =アスパラギン酸アミノトランスフェラーゼ，CPK = クレアチンホスホキナーゼ，CTCAE = NCI 有害事象共通用語規準，ILD = 間質性肺疾患，ULN = 基準値上限
[a] 心拍数60拍/分(bpm)未満

- 特別な集団

肝機能障害
軽度(Child-Pugh A)又は中等度(Child-Pugh B)肝機能障害患者に対して開始用量を調節する必要はない。重度肝機能障害(Child-Pugh C)患者に対する開始用量は，450 mg 1日2回投与とする(総用量900 mg)(5.2を参照)。全ての肝機能障害患者に対し，しかるべきモニタリング(肝機能マーカー等)を行うことが推奨される(4.4を参照)。

腎機能障害
軽度及び中等度腎機能障害患者に対する用量調節は必要ない。重度腎機能障害患者を対象としたアレセンサの試験は行われていない。しかしながら，アレクチニブの腎からの排泄は無視できるため，重度腎機能障害患者において用量調節は必要ない(5.2を参照)。

高齢者(65歳以上)
65歳以上の患者におけるアレセンサの安全性と有効性のデータは限られているが，高齢患者における用量調節の必要性は示唆されていない(5.2を参照)。80歳を超える患者についてはデータが得られていない。

小児集団
小児及び18歳未満の青年におけるアレセンサの安全性と有効性は確立されていない。利用可能なデータはない。

極端な体重(>130 kg)
アレセンサの薬物動態シミュレーションで，極端な体重(>130 kg)の患者における曝露量減少は示されていないが，アレクチニブは広範囲に分布し，アレクチニブの臨床試験に登録された患者の体重は36.9～123 kg の範囲であった。体重が130 kg を超える患者についてはデータが得られていない。

- 投与方法

アレセンサは経口投与する。硬カプセル剤をそのまま飲み込むこと。カプセルを開封したり溶解したりしてはならない。服用は食事とともに行わなければならない(5.2を参照)。

4.3　禁忌
アレクチニブ又は6.1記載の添加剤に対する過敏症

[6.1 添加剤の一覧]

<u>カプセル内容物</u>
乳糖水和物
ヒドロキシプロピルセルロース
ラウリル硫酸ナトリウム

ステアリン酸マグネシウム
カルメロースカルシウム

カプセルシェル
ヒプロメロース
カラギーナン
塩化カリウム
酸化チタン(E171)
トウモロコシデンプン
カルナバロウ

印刷用インク
赤色酸化鉄(E172)
黄色酸化鉄(E172)
インジゴカルミンアルミニウムレーキ(E132)
カルナバロウ
白色セラック
モノオレイン酸グリセリン

4.4　警告及び使用上の注意

- 間質性肺疾患(ILD)/肺臓炎

アレセンサの臨床試験において，ILD/肺臓炎の症例が報告されている(4.8を参照)。肺臓炎を示唆する肺症状がないかどうか患者を観察すること。ILD/肺臓炎と診断された患者ではアレセンサの投与を直ちに中断し，ILD/肺臓炎の他の原因の可能性が特定されなかった場合は投与を永続的に中止すること(4.2を参照)。

- 肝毒性

アレセンサのピボタル試験において，アラニンアミノトランスフェラーゼ(ALT)とアスパラギン酸アミノトランスフェラーゼ(AST)の5×ULN を超える増加，及びビリルビンの3×ULN を超える増加が発現している(4.8を参照)。これら事象の大部分は，投与開始後最初の3カ月以内に発現したものであった。アレセンサのピボタル試験では，Grade 3～4の AST/ALT 増加がみられた患者3例において薬物性肝障害が報告された。アレセンサの臨床試験で投与が行われた1例において，ALT 又は AST の3×ULN 以上の増加と総ビリルビンの2×ULN 以上の増加が同時にみられたが，アルカリホスファターゼは正常値であった。

肝機能(ALT，AST 及び総ビリルビンを含む)を，ベースライン及び以後，投与開始後最初の3カ月間は2週間に1回観察すること。3カ月後以降に事象が発現することもあるため，それ以後も観察を定期的に行い，アミノトランスフェラーゼとビリルビンの増加があらわれた患者ではより頻回に検査を行うこと。この副作用の重症度に基づき，表2記載の通りアレセンサを休薬し，減量した用量で投与を再開するか，又は永続的に中止すること(4.2を参照)。

- 重度の筋肉痛及びクレアチンホスホキナーゼ(CPK)増加

アレセンサのピボタル試験において，筋肉痛又は筋骨格痛(Grade 3の事象を含む)が報告された(4.8を参照)。

アレセンサのピボタル試験において，CPK 増加(Grade 3の事象を含む)が発現した(4.8を参照)。NP28761，NP28673, BO28984及び BO40336試験において，Grade 3の CPK 増加が発現するまでの期間の中央値は15日であった。

患者に対して，原因不明の筋肉痛，圧痛又は脱力があらわれた場合は報告するよう指導すること。CPK 値を，投与開始後最初の1カ月間は2週間に1回，及び症状が報告された患者では臨床的必要性に応じて評価すること。CPK 増加の重症度に基づき，アレセンサを休薬し，その後投与を再開するか，又は用量を減量する(4.2を参照)。

- 徐脈

アレセンサの投与に伴い，症候性徐脈が発現する可能性がある(4.8を参照)。臨床的必要性に応じて心拍数と血圧をモニタリングすること。無症候性徐脈の場合，用量変更の必要はない(4.2を参照)。症候性徐脈又は生命を脅かす事象が発現した患者では，徐脈をもたらすことが知られている併用薬と高血圧治療薬を調べ，表2記載の通りアレセンサの投与を調節すること(4.2及び4.5「P-gp 基質」及び「BCRP 基質」を参照)。

- 溶血性貧血

アレセンサを投与した患者に溶血性貧血が報告されている(4.8項参照)。ヘモグロビン濃度が10 g/dL 未満で溶血性貧血が疑われる場合は，アレセンサの投与を中断し，適切な臨床検査を開始すること。溶血性貧血が確認された場合は，表2に従い，回復後に減量してアレセンサの投与を再開する(4.2項参照)。

- 消化管穿孔

アレセンサを投与した高リスク患者(憩室炎の既往，消化管への転移，消化管穿孔のリスクが認識されている医薬品の併用)で消化管穿孔の症例が報告されている。消化管穿孔が発現した患者では，アレセンサの投与中止を検討すること。消化管穿孔の徴候及び症状について患者に説明し，発現した場合は速やかに相談するよう指導すること。

- 光線過敏症

アレセンサ投与に伴い，日光に対する光線過敏症が報告されている(4.8を参照)。患者に対し，アレセンサ投与中及び投与中止後少なくとも7日間は日光に長時間当たらないよう指導すること。また，日焼け防止のため，スペクトルのカバー範囲が広い紫外線 A(UVA)/紫外線 B(UVB)日焼け止めとリップクリーム(SPF≧50)を使用するよう指導すること。

- 妊娠可能な女性

アレセンサは，妊婦に投与すると胎児に有害となる可能性がある。アレセンサを服用する妊娠可能な女性は，投与期間中及び最終投与後少なくとも3カ月間にわたり，効果の高い避妊法を使用しなければならない(4.6及び5.3を参照)。

- ラクトース不耐性

本薬は乳糖を含有する。まれな遺伝性障害であるガラクトース不耐症，先天性ラクターゼ欠乏症又はグルコース・ガラクトース吸収不良症の患者には，本薬を投与しないこと。

- ナトリウム含量

本薬1日量(1200 mg)はナトリウムを48 mg 含有する。これは，WHO が推奨する成人の最高1日摂取量であるナトリウム2 g の2.4%に相当する。

4.5　他剤との相互作用及び他の形態の相互作用

- 他の医薬品がアレクチニブに及ぼす影響

in vitro データに基づくと，CYP3A4はアレクチニブとその主要活性代謝物 M4の両方の代謝を仲介する主要酵素であり，CYP3A は総肝代謝の40%~50%に寄与する。M4は ALK に対して同様の *in vitro* 効力及び活性を示した。

CYP3A 誘導剤

強力な CYP3A 誘導剤であるリファンピシン600 mg の1日1回反復経口投与とアレクチニブ600 mg の単回経口投与を併用したとき，アレクチニブの C_{max} 及び AUC_{inf} はそれぞれ51%及び73%減少し，M4の C_{max} 及び AUC_{inf} はそれぞれ2.20倍及び1.79倍増加した。アレクチニブと M 4の併用による曝露量への影響は小さく，C_{max} 及び AUC_{inf} はそれぞれ4%及び18%減少した。アレクチニブ

と M4の併用曝露量に及ぼす影響を考慮すると，アレセンサを CYP3A 誘導剤と併用投与する場合，用量調節は不要である。強力な CYP3A 誘導剤(カルバマゼピン，フェノバルビタール，フェニトイン，リファブチン，リファンピシン，セントジョーンズワート(セイヨウオトギリソウ)など)を併用している患者については，適切なモニタリングが推奨される。

CYP3A 阻害剤
強力な CYP3A 阻害剤であるポサコナゾール400 mg の1日2回反復経口投与とアレクチニブ300 mg の単回経口投与を併用したとき，アレクチニブの曝露量 C_{max} 及び AUC_{inf} はそれぞれ1.18倍及び1.75倍増加し，M4の C_{max} 及び AUC_{inf} はそれぞれ71%及び25%減少した。アレクチニブと M4の併用曝露量に及ぼす影響は軽微であり，C_{max} は7%低下し，AUC_{inf} は1.36倍増加した。アレクチニブと M4の併用曝露量に及ぼす影響を考慮すると，アレセンサを CYP3A 阻害剤と併用投与する場合，用量調節は不要である。強力な CYP3A 阻害剤(リトナビル，サキナビル，テリスロマイシン，ケトコナゾール，イトラコナゾール，ボリコナゾール，ポサコナゾール，ネファゾドン，グレープフルーツ，セビリアオレンジ等)を併用している患者については適切なモニタリングが推奨される。

胃内 pH を上昇させる医薬品
プロトンポンプ阻害薬であるエソメプラゾール 40 mg1 日 1 回を複数回投与したところ，アレクチニブ及び M4 への複合曝露に対する臨床的に関連する影響は認められなかった。したがって，アレセンサをプロトンポンプ阻害薬や胃内 pH を上昇させる他の医薬品（H2 受容体拮抗薬や制酸薬等）との併用時に用量調節は必要ない。

アレクチニブの体内動態に対するトランスポーターの影響
M4は P 糖蛋白（P-gp）の基質である。アレクチニブは P-gp を阻害するため，P-gp 阻害剤との併用が M4への曝露に対して関連した影響を及ぼすことはないと予想される。

- アレクチニブが他の医薬品に及ぼす影響

CYP の基質
In vitro では，アレクチニブ及び M4は弱い時間依存性の CYP3A4阻害作用を示し，アレクチニブは臨床濃度で弱い CYP3A4及び CYP2B6誘導能を示した。
アレクチニブ 600 mg を複数回投与したところ，感受性 CYP3A 基質であるミダゾラム（2 mg）の曝露量に影響はなかった。したがって，CYP3A 基質の併用投与に関して用量調節は必要ない。CYP3A4は別として，CYP2B6及びプレグナン X 受容体（PXR）制御酵素の誘導リスクは完全には除外できない。経口避妊薬の併用投与の効果が減少する可能性がある。

P-gp 基質
In vitro では，アレクチニブとその主要活性代謝物 M4は排出トランスポーターである P-gp の阻害剤である。したがって，アレクチニブ及び M4は，併用投与された P-gp 基質の血漿中濃度を上昇させる可能性がある。アレセンサを P-gp 基質（ジゴキシン，ダビガトランエテキシラート，トポテカン，シロリムス，エベロリムス，ニロチニブ，ラパチニブ等）と併用投与する場合は，適切なモニタリングを行うことが推奨される。
乳癌耐性タンパク質(BCRP)の基質薬
In vitro では，アレクチニブ及び M4は排出トランスポーターである BCRP の阻害剤である。したがって，アレクチニブ及び M4は，併用投与された BCRP 基質の血漿中濃度を上昇させる可能性がある。アレセンサを BCRP 基質（メトトレキサート，ミトキサントロン，トポテカン，ラパチニブ等）と併用投与する場合は，適切なモニタリングを行うことが推奨される。

4.6　受胎能，妊娠及び授乳

- 妊娠可能な女性/避妊

妊娠可能な女性には，アレセンサ投与中は妊娠を避けるよう指導しなければならない。アレセンサの投与を受ける妊娠可能な女性患者は，投与中及びアレセンサの最終投与後少なくとも3カ月間は，極めて有効な避妊法を使用しなければならない（4.4項及び4.5項参照）。

- 妊娠

アレクチニブを妊婦に使用したデータはないか，限られている。その作用機序に基づき，アレクチニブは妊婦に投与した場合に胎児に有害となる可能性がある。動物を対象とした試験では生殖毒性が示されている（5.3項参照）。
アレセンサ服用中又はアレセンサ最終投与後の3カ月間に妊娠した女性患者は，主治医に連絡しなければならず，また，胎児に有害となる可能性があることについて知らされる必要がある。

- 授乳

アレクチニブ及び／又はその代謝物がヒト母乳中に排泄されるかどうかは不明である。新生児／乳児へのリスクは除外できない。アレセンサ投与中は授乳を控えるよう母親に指導すること。

- 妊孕性

アレクチニブが受胎能に及ぼす影響を評価することを目的とした動物試験は行われていない。一般毒性試験において，雌雄生殖器に対する有害な作用は認められなかった（5.3項参照）。

4.7　自動車運転能力や機械操作能力への影響

アレセンサは自動車の運転及び機械の操作能力に軽度の影響を及ぼす。アレセンサ投与中には症候性徐脈(失神，浮動性めまい，低血圧など)又は視覚障害が発現する可能性があるため，自動車の運転又は機械の操作を行う際は注意すること(4.8項参照)。

4.8　副作用

<u>安全性プロファイルの概要</u>

ALK 陽性の切除後又は進行 NSCLC 患者533例におけるアレセンサの投与を以下に示す。主要な臨床試験では、切除した NSCLC の術後補助療法（BO40336アリナ）又は進行 NSCLC の治療（BO28984, ALEX; NP28761; NP28673）として、これらの患者にアレセンサを推奨用量600 mg1日2回投与した。臨床試験の参加者に関する詳細な情報については5.1項を参照のこと。
BO40336（ALINA;128例）におけるアレセンサの曝露期間の中央値は23.9ヵ月であった。BO28984（ALEX;152例）におけるアレセンサの曝露期間の中央値は28.1ヵ月であり、第 II 相臨床試験（NP28761、NP28673;253例）におけるアレセンサの曝露期間の中央値は11.2ヵ月であった。

主な副作用（ADR）（20%以上）は、便秘、筋肉痛、浮腫、貧血、発疹、ビリルビン増加、ALT 増加及び AST 増加であった。

- 副作用一覧表

各臨床試験でアレセンサの投与を受けた患者に発現した副作用の一覧を Table 3 に示す（BO40336、BO28984、NP28761、NP28673）。

表 3に一覧にした ADR は，以下の規定を用いて定義された器官別大分類及び頻度カテゴリー別に提示している：非常に高頻度（≥1/10），高頻度（≥1/100～<1/10），低頻度（≥1/1,000～<1/100），まれ（≥1/10,000～<1/1,000），非常にまれ（<1/10,000）。各器官別大分類内では，頻度及び重症度の高い順に好ましくない作用を示している。同一の頻度及び重症度の分類内では，重篤度の高い順に副作用を示している。
表3 アレセンサの臨床試験（BO40336、BO28984、NP28761、NP28673；N=533）中及び市販後期間中に報告された ADR

器官別大分類 ADR（MedDRA）	**アレセンサ** **N＝405**	
	頻度カテゴリー **（全 Grade）**	**頻度カテゴリー** **（Grade 3～4）**
血液およびリンパ系障害		
貧血[1)]	非常に高頻度	高頻度
溶血性貧血[2)]	高頻度	–*
神経系障害		
味覚不全[3)]	高頻度	低頻度
眼障害		
視機能障害[4)]	高頻度	–*
心臓障害		
徐脈[5)]	非常に高頻度	–*
呼吸器，胸郭および縦隔障害		
間質性肺疾患／肺臓炎	高頻度	低頻度
胃腸障害		
下痢	非常に高頻度	低頻度
嘔吐	非常に高頻度	低頻度
便秘	非常に高頻度	低頻度
悪心	非常に高頻度	低頻度
口内炎[6)]	高頻度	低頻度
肝胆道系障害		
AST 増加	非常に高頻度	高頻度
ALT 増加	非常に高頻度	高頻度
ビリルビン増加[7)]	非常に高頻度	高頻度
アルカリホスファターゼ増加	非常に高頻度	低頻度
薬物性肝障害[8)]	低頻度	低頻度
皮膚および皮下組織障害		
発疹[9)]	非常に高頻度	高頻度
光線過敏症	高頻度	低頻度
筋骨格系および結合組織障害		
筋肉痛[10)]	非常に高頻度	低頻度
血中クレアチンホスホキナーゼ増加	非常に高頻度	高頻度
腎および尿路障害		
急性腎障害	低頻度	低頻度**
血中クレアチニン増加	高頻度	低頻度**
一般・全身障害および投与部位の状態		
浮腫[11)]	非常に高頻度	低頻度
臨床検査		
体重増加	非常に高頻度	低頻度
代謝及び栄養障害		
高尿酸血症[12)]	高頻度	*

* Grade 3～4 の ADR は認められなかった。
** Grade 5 の事象 1 件を含む（進行 NSCLC 患者で認められた）
1) 貧血、ヘモグロビン減少及び正色素性正球性貧血の症例を含む
2) BO40336 試験で報告された症例（N=128）
3) 味覚不全，味覚減退，味覚障害の症例を含む
4) 霧視，視力障害，硝子体浮遊物，視力低下，眼精疲労，複視，羞明，光視症の症例を含む
5) 徐脈及び洞性徐脈の症例を含む
6) 口内炎及び口腔内潰瘍形成を含む
7) 血中ビリルビン増加，高ビリルビン血症，抱合ビリルビン増加，血中非抱合ビリルビン増加の症例を含む
8) 薬物性肝障害の MedDRA 用語が報告された 2 例，及び肝生検によって薬物性肝障害が記録された Grade 4 の AST 及び ALT 増加が報告された 1 例を含む
9) 発疹，斑状丘疹状皮疹，ざ瘡様皮膚炎，紅斑，全身性皮疹，丘疹性皮疹，そう痒性皮疹，斑状皮疹及び剥脱性発疹の症例を含む
10) 筋肉痛，筋骨格痛及び関節痛の症例を含む
11)末梢性浮腫、浮腫、全身性浮腫、眼瞼浮腫、眼窩周囲浮腫、顔面浮腫、限局性浮腫、末梢腫脹、顔面腫脹、口唇腫脹、腫脹、関節腫脹及び眼瞼腫脹の症例を含む
12)高尿酸血症及び血中尿酸増加の症例を含む

- 主な副作用の説明

間質性肺疾患(ILD)/肺臓炎
臨床試験全体で、アレセンサの投与を受けた患者の1.3%に ILD/肺臓炎が発現し、そのうち0.4%はグレード3であり、0.9%が ILD/肺臓炎により投与を中止した。第 III 相臨床試験 BO28984では，Grade3又は4の ILD/肺臓炎は，アレセンサ投与患者では認められなかったのに対し，クリゾチニブ投与患者では2.0%に認められた。いずれの臨床試験においても，死亡に至った ILD は認められなかった。肺臓炎を示唆する肺症状(4.2項及び4.4項を参照)について患者をモニタリングすること。

肝毒性
臨床試験全体で、3名に薬物性肝障害が認められた（このうち2名では薬物性肝障害が報告され、1名では Grade 4の AST 増加及び ALT 増加が報告され、肝生検で薬物性肝障害が確認されていた）。臨床試験全体で、副作用として AST 増加及び ALT 増加（それぞれ22.7%及び20.1%）がアレセンサの投与を受けた患者に報告されている。これらの事象の大部分は Grade 1又は Grade 2であり、Grade 3以上の事象は AST 増加で3.0%、 ALT 増加で3.2%に報告された。これらの事象は概ね投与開始から3ヵ月以内に発現し，多くは一過性であり，アレセンサの投与中断(それぞれ患者の2.3%及び3.6%で報告された)又は減量(それぞれ1.7%及び1.5%)により回復した。患者の1.1%及び1.3%で，それぞれ AST 及び ALT の上昇によりアレセンサの投与が中止された。
第 III 相臨床試験である BO28984試験では，Grade 3又は4の ALT 又は AST の上昇は，クリゾチニブ投与群で患者の16%及び11%に認められたのに対し，アレセンサ投与群ではそれぞれ患者の5%に認められた。
臨床試験全体では，ビリルビン上昇の副作用が，アレセンサ投与群の患者の25.1%で報告された。これらの事象の大多数は重症度が Grade 1及び2であり，Grade 3の事象は患者の3.4%で報告された。これらの事象は概ね投与開始後最初の3カ月間に発現し，通常は一過性であり，大多数は用量変更により回復した。患者の7.7%でビリルビン上昇が用量変更に至り，患者の1.5%でビリルビン上昇によってアレセンサの投与中止に至った。第 III 相臨床試験である BO28984試験では，

Grade 3又は4のビリルビン上昇は，アレセンサ群の患者の3.9%で発現したのに対し，クリゾチニブ群の患者では認められなかった。
アレセンサの臨床試験では，投与患者1例（0.2%）で，ALT 又は AST が ULN の3倍以上，総ビリルビンが ULN の2倍以上に同時に上昇し，アルカリホスファターゼは正常であった。

4.4項に記載したとおり，ALT，AST 及び総ビリルビンを含む肝機能をモニタリングし，4.2項の推奨事項に従って管理する。

徐脈
臨床試験全体では，アレセンサ投与群の患者で Grade 1又は2の徐脈（11.1%）が報告されている。重症度が Grade 3以上の事象が発現した患者はいなかった。アレセンサ投与群の521例中102例（19.6%）で投与後の心拍数が50拍/分（bpm）未満であった。第 III 相臨床試験 BO28984では，投与後の心拍数が50 bpm 未満であった患者は，アレセンサ投与群では患者の15%であったのに対し，クリゾチニブ投与群では患者の21%であった。症候性徐脈を発症した患者は，4.2項及び4.4項の推奨どおりに管理すること。徐脈によってアレセンサの投与中止に至った症例はない。

重度の筋肉痛及び CPK 増加
臨床試験全体では，アレセンサを投与された患者で，筋肉痛事象（24%）を含む筋肉痛（34.9%），関節痛（16.1%），筋骨格痛（0.9%）の症例が報告されている。事象の大多数は Grade 1又は2であり，Grade 3の事象が5例（0.9%）で発現した。これらの有害事象によってアレセンサの用量変更が必要となったのは9例（1.7%）のみであり，これらの筋肉痛の事象によってアレセンサが投与中止となることはなかった。アレセンサの臨床試験全体では，CPK の臨床検査データが得られた491例中55.6%で CPK の上昇がみられた。Grade 3以上の CPK 上昇の発現率は5.5%であった。Grade 3以上の CPK 上昇の発現までの期間の中央値は，臨床試験全体で15日であった。CPK の上昇によって患者の5.3%で用量が変更になり，CPK 上昇によるアレセンサの投与中止は認められなかった。臨床試験 BO28984では，アレクチニブ群の1例（0.7%）及びクリゾチニブ群の2例（1.3%）で重度の関節痛が報告された。Grade 3以上の CPK の上昇は，アレセンサ群の3.9%及びクリゾチニブ群の3.3%で報告された。

溶血性貧血
臨床試験でアレセンサの投与を受けた患者の3.1%に溶血性貧血が認められた。これらは Grade 1又は2（非重篤）であり、投与中止には至らなかった（4.2項及び4.4項参照）。

消化管への影響
便秘（38.6%），悪心（17.4%），下痢（17.4%）及び嘔吐（12%）が最も多く報告された消化管（GI）反応であった。これらの事象の大半は重症度が軽度又は中等度であり，Grade 3の事象が下痢（0.9%），悪心（0.4%），嘔吐（0.2%）及び便秘（0.4%）で報告された。これらの事象によってアレセンサの投与中止には至らなかった。臨床試験全体では，便秘，悪心，下痢，及び／又は嘔吐の発現までの期間の中央値は21日であった。これらの事象は投与開始の1カ月後以降に頻度が低下した。第 III 相臨床試験 BO28984では，Grade 3及び4の悪心，下痢及び便秘の事象がアレクチニブ群の各1例（0.7%）で報告され，Grade 3及び4の悪心，下痢及び嘔吐の事象の発現率は，クリゾチニブ群でそれぞれ3.3%，2.0%及び3.3%であった。

副作用が疑われた場合の報告
医薬品承認後，その医薬品のベネフィット／リスクバランスを継続的にモニタリングするためには，副作用と疑われた事象を報告することが重要である。医療従事者は，副作用と疑われた事象を全て，Appendix V 記載の国の報告制度を通じて報告されたい。

4.9　過量投与

過量投与がみられた患者には十分な管理を行い，一般的な支持療法を開始すること。アレセンサの過量投与に対する特定の解毒剤はない。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALECENSA safely and effectively. See full prescribing information for ALECENSA.

ALECENSA® (alectinib) capsules, for oral use
Initial U.S. Approval: 2015

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	04/2024
Dosage and Administration (2.1, 2.2, 2.3)	04/2024
Warnings and Precautions (5)	04/2024

---------- INDICATIONS AND USAGE----------

ALECENSA is a kinase inhibitor indicated for:

- 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 an FDA-approved test. (1.1)
- treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test. (1.2)

----------DOSAGE AND ADMINISTRATION----------

600 mg orally twice daily. Administer ALECENSA with food. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

Capsules: 150 mg (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS----------

- Hepatotoxicity: Monitor liver laboratory tests every 2 weeks during the first 3 months of treatment, then once a month and as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations. In case of severe ALT, AST, or bilirubin elevations, withhold, then reduce dose, or permanently discontinue ALECENSA. (2.4, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Immediately withhold ALECENSA in patients diagnosed with ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis have been identified. (2.4, 5.2)
- Renal Impairment: Withhold ALECENSA for severe renal impairment, then resume ALECENSA at reduced dose upon recovery or permanently discontinue (2.4, 5.3).
- Bradycardia: Monitor heart rate and blood pressure regularly. If symptomatic, withhold ALECENSA then reduce dose, or permanently discontinue. (2.4, 5.4)
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation: Assess CPK every 2 weeks during the first month of treatment and in patients reporting unexplained muscle pain, tenderness, or weakness. In case of severe CPK elevations, withhold, then resume or reduce dose. (2.4, 5.5)
- Hemolytic Anemia: If hemolytic anemia is suspected, withhold ALECENSA. If hemolytic anemia is confirmed, consider resuming at a reduced dose upon resolution or permanently discontinue. (5.6)
- Embryo-Fetal Toxicity: ALECENSA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (incidence ≥20%) were hepatotoxicity, constipation, fatigue, myalgia, edema, rash and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Adjuvant Treatment of Resected ALK-Positive NSCLC
1.2 Treatment of Metastatic ALK-Positive NSCLC
2 DOSAGE AND ADMINISTRATION
2.1 Patient Selection
2.2 Dosing and Administration
2.3 Recommended Dosage for Hepatic Impairment
2.4 Dose Modifications for Adverse Reactions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hepatotoxicity
5.2 Interstitial Lung Disease (ILD)/Pneumonitis
5.3 Renal Impairment
5.4 Bradycardia
5.5 Severe Myalgia and Creatine Phosphokinase (CPK) Elevation
5.6 Hemolytic Anemia
5.7 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Adjuvant Treatment of Resected ALK-Positive NSCLC
14.2 Treatment of Metastatic ALK-Positive NSCLC
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 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 an FDA-approved test *[see Dosage & Administration (2.1)]*.

1.2 Treatment of Metastatic ALK-Positive NSCLC

ALECENSA is indicated for the treatment of adult patients with ALK-positive metastatic NSCLC as detected by an FDA-approved test *[see Dosage & Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with resectable tumors for the adjuvant treatment of NSCLC with ALECENSA based on the presence of ALK positivity in tumor tissue *[see Indications and Usage (1.1) and Clinical Studies (14.1)]*.

Select patients for the treatment of metastatic NSCLC with ALECENSA based on the presence of ALK positivity in tumor tissue or plasma specimens *[see Indications and Usage (1.2) and Clinical Studies (14.2)]*. If ALK rearrangements are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Dosing and Administration

The recommended dosage information for ALECENSA is provided in Table 1.

Table 1: ALECENSA Recommended Dosage and Duration of Treatment

<table>
<tr><th>Indication</th><th>Recommended Dosage of ALECENSA</th><th>Duration</th></tr>
<tr><td>Adjuvant treatment of resected NSCLC</td><td rowspan="2">600 mg orally twice daily with food
[see Clinical Pharmacology (12.3)]</td><td>For a total of 2 years or until disease recurrence or unacceptable toxicity</td></tr>
<tr><td>Metastatic NSCLC</td><td>Until disease progression or unacceptable toxicity</td></tr>
<tr><td colspan="3">• Swallow capsules whole, do not open or dissolve the contents of the capsule.
• If a dose of ALECENSA is missed or vomiting occurs after taking a dose of ALECENSA, take the next dose at the scheduled time.</td></tr>
</table>

2.3 Recommended Dosage for Hepatic Impairment

The recommended dose of ALECENSA in patients with severe hepatic impairment (Child-Pugh C) is 450 mg orally twice daily *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.4 Dose Modifications for Adverse Reactions

The dose reduction schedule for ALECENSA is provided in Table 2.

Table 2: ALECENSA Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting dose	600 mg taken orally twice daily
First dose reduction	450 mg taken orally twice daily
Second dose reduction	300 mg taken orally twice daily

Discontinue if patients are unable to tolerate the 300 mg twice daily dose.

Recommendations for dose modifications of ALECENSA in case of adverse reactions are provided in Table 3.

Table 3: ALECENSA Dose Modifications for Adverse Reactions

Criteria[a]	ALECENSA Dose Modification
ALT or AST elevation of greater than 5 times upper limit of normal (ULN) with total bilirubin less than or equal to 2 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 3 times ULN, then resume at reduced dose as per Table 2.
ALT or AST elevation greater than 3 times ULN with total bilirubin elevation greater than 2 times ULN in the absence of cholestasis or hemolysis	Permanently discontinue ALECENSA.
Total bilirubin elevation of greater than 3 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 1.5 times ULN, then resume at reduced dose as per Table 2.
Any grade treatment-related interstitial lung disease (ILD)/pneumonitis	Permanently discontinue ALECENSA.
Grade 3 renal impairment	Temporarily withhold until serum creatinine recovers to less than or equal to 1.5 times ULN, then resume at reduced dose.
Grade 4 renal impairment	Permanently discontinue ALECENSA.
Symptomatic bradycardia	Withhold ALECENSA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ALECENSA at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume ALECENSA at reduced dose (see Table 2) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.
Bradycardia[b] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue ALECENSA if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume ALECENSA at reduced dose (see Table 2) upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with

	frequent monitoring as clinically indicated. Permanently discontinue ALECENSA in case of recurrence.
CPK elevation greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	Temporarily withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose as per Table 2.
Hemolytic Anemia	Withhold ALECENSA if hemolytic anemia is suspected. Upon resolution, resume at reduced dose or permanently discontinue.

[a] ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal; ILD = interstitial lung disease; CPK = blood creatine phosphokinase

[b] Heart rate less than 60 beats per minute (bpm)

3 DOSAGE FORMS AND STRENGTHS

150 mg hard capsules, white, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Severe hepatotoxicity, including drug-induced liver injury, occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]* of patients who received ALECENSA, hepatotoxicity occurred in 41% of patients and the incidence of Grade ≥ 3 hepatotoxicity was 8%. In the ALINA study, hepatotoxicity occurred in 61% of patients treated with ALECENSA and the incidence of Grade ≥ 3 hepatotoxicity was 4.7%. The majority (72% of 136 patients) of elevated transaminases occurred during the first 3 months of treatment. Treatment discontinuation due to hepatotoxicity occurred in 3.6% of patients who received ALECENSA in the pooled safety population and 1.6% of patients treated in the ALINA study.

In the pooled safety population, concurrent elevations in ALT or AST greater than or equal to 3 times the ULN and total bilirubin greater than or equal to 2 times the ULN, with normal alkaline phosphatase, occurred in less than 1% of patients treated with ALECENSA. Three patients with Grades 3–4 AST/ALT elevations had drug-induced liver injury (documented by liver biopsy in two cases).

Monitor liver function tests including ALT, AST, and total bilirubin every 2 weeks during the first 3 months of treatment, then once a month and as clinically indicated, with more frequent testing in patients who develop transaminase and bilirubin elevations. Based on the severity of the adverse drug reaction, withhold ALECENSA and resume at a reduced dose or permanently discontinue ALECENSA as described in Table 3 *[see Dosage and Administration (2.4)]*.

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, ILD/pneumonitis occurred in 1.3% of patients treated with ALECENSA with 0.4% of patients experiencing Grade 3 ILD/pneumonitis.

Five patients (0.9%) in the pooled safety population discontinued ALECENSA due to ILD/pneumonitis. The median time-to-onset of Grade 3 or higher ILD/pneumonitis was 2.1 months (range: 0.6 months to 3.6 months).

Promptly investigate for ILD/pneumonitis in any patient who presents with worsening of respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, and fever). Immediately withhold ALECENSA treatment in patients diagnosed with ILD/pneumonitis and permanently discontinue ALECENSA if no other potential causes of ILD/pneumonitis have been identified *[see Dosage and Administration (2.4) and Adverse Reactions (6)]*.

5.3 Renal Impairment

Renal impairment, including fatal cases, occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, renal impairment occurred in 12% of patients treated with ALECENSA, including Grade ≥ 3 in 1.7% of patients, of which 0.4% were fatal events. The median time to Grade ≥ 3 renal impairment was 3.7 months (range 0.5 to 31.8 months). Dosage modifications for renal impairment were required in 2.4% of patients.

Permanently discontinue ALECENSA for Grade 4 renal toxicity. Withhold ALECENSA for Grade 3 renal toxicity until recovery to less than or equal to 1.5 times ULN, then resume at reduced dose *[see Dosage and Administration (2.4)]*.

5.4 Bradycardia

Symptomatic bradycardia occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, bradycardia occurred in 11% of patients treated with ALECENSA. Twenty percent of 521 patients treated with ALECENSA, for whom serial electrocardiograms (ECGs) were available, had post-dose heart rates of less than 50 beats per minute (bpm).

Monitor heart rate and blood pressure regularly. For asymptomatic bradycardia dose modification is not required. For symptomatic bradycardia that is not life-threatening, withhold ALECENSA until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm and evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If bradycardia is attributable to a concomitant medication, resume ALECENSA at a reduced dose (see Table 2) upon recovery to asymptomatic bradycardia or to a heart rate of ≥ 60 bpm, with frequent monitoring as clinically indicated.

Permanently discontinue ALECENSA in cases of life-threatening bradycardia if no contributing concomitant medication is identified *[see Dosage and Administration (2.4)]*. Permanently discontinue ALECENSA for recurrence of life-threatening bradycardia.

5.5 Severe Myalgia and Creatine Phosphokinase (CPK) Elevation

Severe myalgia and creatine phosphokinase (CPK) elevation occurred in patients treated with ALECENSA.

In the pooled safety population *[see Adverse Reactions (6.1)]*, myalgia (including muscle- and musculoskeletal-related reactions) occurred in 31% of patients treated with ALECENSA, including Grade ≥ 3 in 0.8% of patients. Dosage modifications for myalgia events were required in 2.1% of patients.

In the pooled safety population, of the 491 patients with CPK laboratory data available, elevated CPK occurred in 56% of patients treated with ALECENSA, including 6% Grade ≥ 3. The median time to Grade ≥ 3 CPK elevation was 15 days (interquartile range - 15 –337 days). Dosage modifications for elevation of CPK occurred in 5% of patients.

In the ALINA study, elevated CPK occurred in 77% of 128 patients with CPK laboratory data, including 6% Grade ≥ 3 elevations.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Assess CPK levels every 2 weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the

severity of the CPK elevation, withhold ALECENSA, then resume or reduce dose *[see Dosage and Administration (2.4)]*.

5.6 Hemolytic Anemia

Hemolytic anemia occurred in patients treated with ALECENSA.

Hemolytic anemia was initially reported with ALECENSA in the postmarketing setting, including cases associated with a negative direct antiglobulin test (DAT) result. Assessments for the determination of hemolytic anemia were subsequently collected in the ALINA study, where hemolytic anemia was observed in 3.1% of patients treated with ALECENSA. If hemolytic anemia is suspected, withhold ALECENSA and initiate appropriate laboratory testing. If hemolytic anemia is confirmed, consider resuming at a reduced dose upon resolution or permanently discontinue ALECENSA *[see Dosage and Administration (2.4)]*.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to pregnant women. Oral administration of alectinib to pregnant rats and rabbits during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7-fold those observed in humans with alectinib 600 mg twice daily. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 5 weeks following the last dose *[see Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*
- Renal Impairment *[see Warnings and Precautions (5.3)]*
- Bradycardia *[see Warnings and Precautions (5.4)]*
- Severe Myalgia and Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.5)]*
- Hemolytic Anemia *[see Warnings and Precautions (5.6)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to ALECENSA as a single agent at 600 mg orally twice daily in 533 patients in Studies NP28761, NP28673, ALEX and ALINA *[see Clinical Studies (14)]*. Among 533 patients who received ALECENSA, 75% were exposed for 6 months or longer and 64% were exposed for greater than one year. In this pooled safety population, the most common (≥ 20%) adverse reactions were hepatotoxicity (41%), constipation (39%), fatigue (36%), myalgia (31%), edema (29%), rash (23%) and cough (21%). The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were increased CPK (6%), decreased hemoglobin (4.4%), increased ALT (4.2%), increased bilirubin (4.0%) and increased AST (3.4%).

Adjuvant Treatment of Resected ALK-Positive NSCLC

The safety of ALECENSA was evaluated in ALINA, a multi-center, open-label, randomized trial for the adjuvant treatment of patients with resected ALK-positive NSCLC [*see Clinical Studies (14.1)*]. At the time of DFS analysis, the median duration of exposure was 23.9 months for ALECENSA and 2.1 months for platinum-based chemotherapy.

Serious adverse reactions occurred in 13% of patients treated with ALECENSA; the most frequent serious adverse reactions (≥ 1%) were pneumonia (3.9%), appendicitis (3.1%), and acute myocardial infarction (1.6%). Permanent discontinuation of ALECENSA due to an adverse event occurred in 5% of patients; the most frequent adverse reactions (≥ 1%) that led to treatment discontinuation were pneumonitis and hepatotoxicity.

Dosage interruptions of ALECENSA due to an adverse reaction occurred in 27% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients included hepatotoxicity, increased blood CPK, COVID-19, myalgia, abdominal pain, and pneumonia.

Dose reductions of ALECENSA due to an adverse reaction occurred in 26% of patients. Adverse reactions which required dose reductions in ≥ 2% of patients included hepatotoxicity, increased blood CPK, rash, bradycardia and myalgia.

Table 4 and 5 summarize the common adverse reactions and laboratory abnormalities observed in ALINA.

Table 4: Adverse Reactions (≥ 10%) in Patients Treated with ALECENSA in ALINA

Adverse Reaction	ALECENSA N=128		Chemotherapy N=120	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hepatobiliary System Disorders				
Hepatotoxicity[a]	61	4.7*	13	0
Gastrointestinal Disorders				
Constipation	42	0.8*	25	0.8*
Abdominal pain[b]	13	0	10	1.7*
Diarrhea[c]	13	0.8*	9	1.7*
Musculoskeletal				
Myalgia[d]	34	0.8*	1.7	0
Infections and Infestations				
COVID-19	29	0	0.8	0
General Disorders and Administration Site Conditions				
Fatigue[e]	25	0.8*	28	4.2*
Edema[f]	16	0	1.7	0
Skin and Subcutaneous Tissue Disorders				
Rash[g]	23	1.6*	10	0
Respiratory System Disorders				
Cough[h]	20	0.8*	3.3	0
Dyspnea[i]	13	0.8*	2.5	0
Renal				
Renal Impairment[j]	16	0.8*	9	0

Nervous System Disorders				
Dysgeusia[k]	13	0	3.3	0
Headache	11	0	7	0
Investigations				
Increased weight	13	0.8[*]	0.8	0
Cardiac Disorders				
Bradycardia[l]	12	0	0	0

Based on NCI CTCAE v5.0

[*] All events are Grade 3.

[a] Includes increased alanine aminotransferase, increased aspartate aminotransferase, increased bile acids, increased conjugated bilirubin, increased blood bilirubin, increased unconjugated blood bilirubin, increased gamma-glutamyltransferase, hepatotoxicity, hyperbilirubinemia, increased liver function test, ocular icterus and increased transaminases.

[b] Includes abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain, abdominal tenderness, epigastric discomfort and gastrointestinal pain.

[c] Includes colitis and diarrhea.

[d] Includes muscle fatigue, muscular weakness, musculoskeletal chest pain, musculoskeletal stiffness and myalgia.

[e] Includes asthenia and fatigue.

[f] Includes edema, face edema, localized edema, peripheral edema, face swelling and peripheral swelling.

[g] Includes acneiform dermatitis, bullous dermatitis, drug eruption, eczema, rash, erythematous rash, maculo-papular rash, papular rash, seborrheic dermatitis, urticaria and xeroderma.

[h] Includes cough and productive cough.

[i] Includes dyspnea and exertional dyspnea.

[j] Includes azotemia, increased blood creatinine, decreased renal creatinine clearance, decreased glomerular filtration rate, hypercreatininemia, renal impairment and renal failure.

[k] Includes dysgeusia and taste disorder.

[l] Includes bradycardia and sinus bradycardia.

Clinically significant adverse reactions in < 10% of patients who received ALECENSA in ALINA: nausea (8%), vomiting (7%), vision disorders (4.7%; includes blurred vision, visual acuity reduced and photopsia), stomatitis (4.7%; includes stomatitis and mouth ulceration), photosensitivity reaction (3.9%) and pneumonitis (2.3%).

Table 5: Worsening in Laboratory Values from Baseline Occurring in ≥ 20% of Patients in Treated with ALECENSA in ALINA

Parameter	ALECENSA N=128		Chemotherapy N=120	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Increased CPK	77	8	8	1.7*
Increased AST	75	0.8*	25	0
Increased bilirubin	68	2.3*	4.2	0
Increased alkaline phosphatase	64	0	14	0
Increased ALT	57	2.3*	28	0
Increased creatinine	41	0	23	0
Increased uric acid	30	0	19	0
Hematology				
Decreased hemoglobin	69	0	67	0.8*

Based on NCI CTCAE v5.0
*All events were Grade 3

Previously Untreated Metastatic ALK-Positive NSCLC

The safety of ALECENSA was evaluated in 152 patients with ALK-positive NSCLC in the ALEX study. The median duration of exposure to ALECENSA was 17.9 months. Patient characteristics of the ALEX study population (n=303) were: median age 56 years, age less than 65 (77%), female (56%), Caucasian (50%), Asian (46%), adenocarcinoma histology (92%), never smoker (63%), and ECOG PS 0 or 1 (93%).

Serious adverse reactions occurred in 28% of patients treated with ALECENSA; serious adverse reactions reported in 2% or more of patients treated with ALECENSA were pneumonia (4.6%), and renal impairment (3.9%). Grade ≥ 3 adverse events were reported for 41% of patients in the ALECENSA arm. Fatal adverse reactions occurred in 3.3% of patients treated with ALECENSA; these were renal impairment (2 patients), sudden death, cardiac arrest, and pneumonia (1 patient each). Permanent discontinuation of ALECENSA for adverse reactions occurred in 11% of patients. Adverse drug reactions that led to discontinuation of ALECENSA in 1% or more of patients were renal impairment (2.0%), hyperbilirubinemia (1.3%), increased ALT (1.3%), and increased AST (1.3%). Dosage interruptions of ALECENSA due to an adverse reaction occurred in 20% of patients. Adverse reactions which required dosage interruption in > 2% of patients included increased ALT, pneumonia. Dose reductions of ALECENSA due to an adverse reaction occurred in 17% of patients. Adverse reactions which required dose reductions in > 2% of patients included hyperbilirubinemia, increased AST and increased ALT.

Tables 6 and 7 summarize the common adverse reactions and laboratory abnormalities observed in ALEX.

Table 6: Adverse Drug Reactions (>10% for all NCI CTCAE Grades or ≥2% for Grades 3-4) in Patients Treated with ALECENSA in ALEX

Adverse Reaction	ALECENSA N=152		Crizotinib N=151	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Constipation	34	0	33	0
Nausea	14	0.7	48	3.3
Diarrhea	12	0	45	2.0
General				
Fatigue[a]	26	1.3	23	0.7
Edema[b]	22	0.7	34	0.7
Musculoskeletal				
Myalgia[c]	23	0	4.0	0
Skin				
Rash[d]	15	0.7	13	0
Cardiac				
Bradycardia[e]	11	0	15	0
Renal				
Renal impairment[f]	12	3.9*	0	0

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class.

[a] Includes fatigue and asthenia.

[b] Includes peripheral edema, edema, eyelid edema, localized edema, and face edema.

[c] Includes myalgia and musculoskeletal pain.

[d] Includes rash, rash maculo-papular, dermatitis acneiform, erythema, generalized rash, rash macular, rash papular, exfoliative rash, and pruritic rash.

[e] Includes reported cases of bradycardia and sinus bradycardia but is not based on serial ECG assessment.

[f] Includes increased blood creatinine, creatinine renal clearance decreased, glomerular filtration rate decreased, and acute kidney injury.

* Includes two Grade 5 events.

The following additional clinically significant adverse drug reactions were observed in patients treated with ALECENSA: weight gain (9.9%), vomiting (7%), photosensitivity reaction (5.3%), vision disorders (4.6%; includes blurred vision, visual impairment, vitreous floaters reduced visual acuity and diplopia), stomatitis (3.3%), dysgeusia (3.3%; includes hypogeusia), interstitial lung disease (1.3%), and drug-induced liver injury (1.3%).

Table 7: Worsening in Laboratory Values Occurring in > 10% of Patients in ALEX

Parameter	ALECENSA N= 152		Crizotinib N=151	
	All Grades (%)	Grades 3–4 (%)	All Grades (%)	Grades 3–4 (%)
Chemistry				
Hyperbilirubinemia[a]	54	5	4.7	0
Increased AST[b]	50	6	56	11
Increased alkaline phosphatase[c]	50	0	44	0
Increased ALT[c]	40	6	62	16
Increased creatinine[c,d]	38	4.1	23	0.7
Increased CPK[e]	37	2.8	52	1.4
Hypocalcemia[a]	29	0	61	1.4
Hyperglycemia[f]	22	2.2	19	2.3
Hyponatremia[g]	18	6	20	4.1
Hypokalemia[c]	17	2	12	0.7
Hypoalbuminemia[h]	14	0	57	3.4
Hyperkalemia[c]	12	1.4	16	1.4
Hypophosphatemia[i]	9	1.4	25	2.7
Increased gamma glutamyl transferase[j]	7	0.7	39	4.1
Hematology				
Anemia[c]	62	7	36	0.7
Lymphopenia[a]	14	1.4	34	4.1
Neutropenia[c]	14	0	36	7

Note: Based on National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
Excludes patients with no post-baseline lab assessments.
[a] n=147 for alectinib (with baseline values missing for 1 of these patients), n=148 for crizotinib.
[b] n=147 for alectinib (with baseline values missing for 2 of these patients), n=148 for crizotinib.
[c] n=147 for alectinib, n=148 for crizotinib.
[d] Only patients with creatinine increases based on ULN definition.
[e] n=143 for alectinib (with baseline values missing for 14 of these patients), n=143 for crizotinib (with baseline values missing for 13 of these patients).
[f] n=134 for alectinib (with baseline values missing for 18 of these patients), n=131 for crizotinib (with baseline values missing for 8 of these patients).
[g] n=147 for alectinib, n=148 for crizotinib (with baseline values missing for 1 of these patients).
[h] n=146 for alectinib (with baseline values missing for 1 of these patients), n=148 for crizotinib (with baseline values missing for 1 of these patients).
[i] n=145 for alectinib (with baseline values missing for 2 of these patients), n=148 for crizotinib (with baseline values missing for 4 of these patients).
[j] n=143 for alectinib (with baseline values missing for 4 of these patients), n=148 (with baseline values missing for 5 of these patients).

Metastatic ALK-Positive NSCLC Previously Treated with Crizotinib

The safety of ALECENSA was evaluated in 253 patients with ALK-positive non-small cell lung cancer (NSCLC) treated with ALECENSA in two clinical trials, Studies NP28761 and NP28673. The median duration of exposure to ALECENSA was 9.3 months. One hundred sixty-nine patients (67%) were exposed to ALECENSA for more than 6 months, and 100 patients (40%) for more than one year. The population characteristics were: median age 53 years, age less than 65 (86%), female (55%), White (74%), Asian (18%), NSCLC adenocarcinoma histology (96%), never or former smoker (98%), ECOG Performance Status (PS) 0 or 1 (91%), and prior chemotherapy treatment (78%).

Serious adverse reactions occurred in 19% of patients; the most frequently reported serious adverse reactions were pulmonary embolism (1.2%), dyspnea (1.2%), and hyperbilirubinemia (1.2%). Fatal adverse reactions occurred in 2.8% of patients and included hemorrhage (0.8%), intestinal perforation (0.4%), dyspnea (0.4%),

pulmonary embolism (0.4%), and endocarditis (0.4%). Permanent discontinuation of ALECENSA for adverse reactions occurred in 6% of patients. The most frequent adverse reactions that led to permanent discontinuation were hyperbilirubinemia (1.6%), increased ALT levels (1.6%), and increased AST levels (1.2%). Overall, 23% of patients initiating treatment at the recommended dose required at least one dose reduction. The median time to first dose reduction was 48 days. The most frequent adverse reactions that led to dose reductions or interruptions were elevations in bilirubin (6%), CPK (4.3%), ALT (4.0%), AST (2.8%), and vomiting (2.8%).

Tables 8 and 9 summarize the common adverse reactions and laboratory abnormalities observed in Studies NP28761 and NP28673.

Table 8: Adverse Reactions in ≥ 10% (All Grades) or ≥ 2% (Grades 3–4) of Patients in Studies NP28761 and NP28673

Adverse Reactions	**ALECENSA N=253**	
	All Grades (%)	**Grades 3–4 (%)***
Fatigue[a]	41	1.2
Constipation	34	0
Edema[b]	30	0.8
Myalgia[c]	29	1.2
Cough	19	0
Rash[d]	18	0.4
Nausea	18	0
Headache	17	0.8
Diarrhea	16	1.2
Dyspnea	16	3.6[e]
Back pain	12	0
Vomiting	12	0.4
Increased weight	11	0.4
Vision disorder[f]	10	0

* Per Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
[a] Includes fatigue and asthenia.
[b] Includes peripheral edema, edema, generalized edema, eyelid edema, and periorbital edema.
[c] Includes myalgia and musculoskeletal pain.
[d] Includes rash, maculopapular rash, acneiform dermatitis, erythema, generalized rash, papular rash, pruritic rash, and macular rash.
[e] Includes one Grade 5 event.
[f] Includes blurred vision, vitreous floaters, visual impairment, reduced visual acuity, asthenopia, and diplopia.

An additional clinically significant adverse drug reaction was photosensitivity, which occurred in 9.9% of patients exposed to ALECENSA in Studies NP28761 and NP28673. Patients were advised to avoid sun exposure and to use broad-spectrum sunscreen. The incidence of Grade 2 photosensitivity was 0.4%; the remaining events were Grade 1 in severity.

Table 9: Treatment-Emergent Worsening in Laboratory Values Occurring in > 20% of Patients in Studies NP28761 and NP28673

Parameter	ALECENSA N=250	
	All Grades (%)	Grades 3–4 (%)*
Chemistry		
Increased AST	51	3.6
Increased Alkaline Phosphatase	47	1.2
Increased CPK[a]	43	4.6
Hyperbilirubinemia	39	2.4
Hyperglycemia[b]	36	2.0
Increased ALT	34	4.8
Hypocalcemia	32	0.4
Hypokalemia	29	4.0
Increased Creatinine[c]	28	0
Hypophosphatemia	21	2.8
Hyponatremia	20	2.0
Hematology		
Anemia	56	2.0
Lymphopenia[d]	22	4.6

* Per CTCAE version 4.0
[a] n=218 for CPK (with baseline values missing for 91 of these patients).
[b] n=152 for fasting blood glucose (with baseline values missing for 5 of these patients).
[c] Only patients with creatinine increases based on ULN definition.
[d] n=217 for lymphocytes (with baseline values missing for 5 of these patients).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, ALECENSA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on ALECENSA use in pregnant women.

Administration of alectinib to pregnant rats and rabbits by oral gavage during the period of organogenesis resulted in embryo-fetal toxicity and abortion at maternally toxic doses with exposures approximately 2.7-fold those observed in humans treated with alectinib at 600 mg twice daily *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a preliminary rabbit embryo-fetal study, administration of alectinib by oral gavage during the period of organogenesis resulted in abortion or complete embryo-fetal mortality at a maternally toxic dose of 27 mg/kg/day (approximately 2.9-fold the estimated area under the curve ($AUC_{0\text{-}24h,ss}$) in humans treated with alectinib 600 mg twice daily) in three of six pregnant rabbits. The remaining three pregnant rabbits in this group had few live fetuses, decreased fetal and placental weights, and retroesophageal subclavian artery. In a rat preliminary embryo-fetal development study, administration of alectinib during organogenesis resulted in complete litter loss in all pregnant rats at 27 mg/kg/day (approximately 4.5-fold the estimated $AUC_{0\text{-}24h,ss}$ in humans treated with alectinib 600 mg twice daily). Doses greater than or equal to 9 mg/kg/day (approximately 2.7-fold the estimated human $AUC_{0\text{-}24h,ss}$ in humans treated with alectinib 600 mg twice daily), resulted in maternal toxicity as well as developmental toxicities including decreased fetal weight, dilated ureter, thymic cord, small ventricle and thin ventricle wall, and reduced number of sacral and caudal vertebrae.

8.2 Lactation

Risk Summary

There are no data on the presence of alectinib or its metabolites in human milk, the effects of alectinib on the breastfed child, or its effects on milk production. Because of the potential for serious adverse reactions in breastfed children from alectinib, advise a lactating woman not to breastfeed during treatment with ALECENSA and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

ALECENSA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ALECENSA *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 5 weeks after the last dose *[see Use in Specific Populations (8.1)]*.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with ALECENSA and for 3 months following the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ALECENSA in pediatric patients have not been established.

Animal Data

Juvenile animal studies have not been conducted using alectinib. In general toxicology studies, treatment of rats with doses of alectinib resulting in exposures greater than or equal to approximately 4.5-fold those in humans treated with alectinib at 600 mg twice daily resulted in changes in the growing teeth and bones. Findings in teeth included discoloration and changes in tooth size along with histopathological disarrangement of the

ameloblast and odontoblast layers. There were also decreases in the trabecular bone and increased osteoclast activity in the femur and sternum.

8.5 Geriatric Use

Nineteen percent of the 533 patients studied in NP28761, NP28673, ALEX and ALINA were 65 years of age and older (3.2% were 75 years of age and older). No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of serious adverse events (38% vs 25%), more frequent adverse events leading to treatment discontinuations (18% vs 6%) and dose modifications (48% vs 35%) in patients 65 years or older as compared to those younger than 65 years.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment. The safety of ALECENSA in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease has not been studied *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

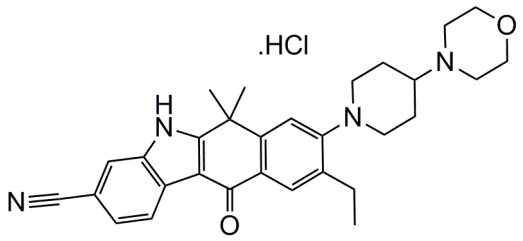
No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Increased exposure of alectinib occurred in patients with severe hepatic impairment (Child-Pugh C). The recommended dose of ALECENSA in patients with severe hepatic impairment (Child-Pugh C) is 450 mg orally twice daily *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

No experience with overdose is available. There is no specific antidote for overdose with ALECENSA. Alectinib and its major active metabolite M4 are > 99% bound to plasma proteins; therefore, hemodialysis is likely to be ineffective in the treatment of overdose.

11 DESCRIPTION

ALECENSA (alectinib) is a kinase inhibitor for oral administration. The molecular formula for alectinib is $C_{30}H_{34}N_4O_2$ • HCl. The molecular weight is 482.62 g/mol (free base form) and 519.08 g/mol (hydrochloride salt). Alectinib is described chemically as 9-ethyl-6, 6-dimethyl-8-[4-(morpholin-4-yl)piperidin-1-yl]-11-oxo-6, 11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile hydrochloride. The chemical structure of alectinib is shown below:



Alectinib HCl is a white to yellow white powder or powder with lumps with a pKa of 7.05 (base).

ALECENSA is supplied as hard capsules containing 150 mg of alectinib (equivalent to 161.33 mg alectinib HCl) and the following inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate, and carboxymethylcellulose calcium. The capsule shell contains hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. The printing ink contains red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alectinib is a tyrosine kinase inhibitor that targets ALK and RET. In nonclinical studies, alectinib inhibited ALK phosphorylation and ALK-mediated activation of the downstream signaling proteins STAT3 and AKT, and decreased tumor cell viability in multiple cell lines harboring ALK fusions, amplifications, or activating mutations. The major active metabolite of alectinib, M4, showed similar in vitro potency and activity.

Alectinib and M4 demonstrated in vitro and in vivo activity against multiple mutant forms of the ALK enzyme, including some mutations identified in NSCLC tumors in patients who have progressed on crizotinib.

In mouse models implanted with tumors carrying ALK fusions, administration of alectinib resulted in antitumor activity and prolonged survival, including in mouse models implanted intracranially with ALK-driven tumor cell lines.

12.2 Pharmacodynamics

Cardiac Electrophysiology

The ability of alectinib to prolong the QT interval was assessed in 221 patients administered ALECENSA 600 mg twice daily in clinical studies. ALECENSA did not prolong the QTc (QT corrected for heart rate) interval to any clinically relevant extent. One patient had a maximum post-baseline QTcF value of greater than 500 msec, and one patient had a maximum QTcF change from baseline of greater than 60 msec.

12.3 Pharmacokinetics

The pharmacokinetics of alectinib and its major active metabolite M4 have been characterized in patients with ALK-positive NSCLC and healthy subjects.

In patients with ALK-positive NSCLC, the geometric mean (coefficient of variation %) steady-state maximal concentration ($C_{max,ss}$) for alectinib was 665 ng/mL (44%) and for M4 was 246 ng/mL (45%) with peak to trough concentration ratio of 1.2. The geometric mean steady-state area under the curve from 0 to 12 hours ($AUC_{0-12h,ss}$) for alectinib was 7,430 ng*h/mL (46%) and for M4 was 2,810 ng*h/mL (46%). Alectinib exposure is dose proportional across the dose range of 460 mg to 900 mg (i.e., 0.75 to 1.5 times the approved recommended dosage) under fed conditions. Alectinib and M4 reached steady-state concentrations by day 7. The geometric mean accumulation was approximately 6-fold for both alectinib and M4.

Absorption

Alectinib reached maximal concentrations at 4 hours following administration of ALECENSA 600 mg twice daily under fed conditions in patients with ALK-positive NSCLC.

The absolute bioavailability of alectinib was 37% (90% CI: 34%, 40%) under fed conditions.

A high-fat, high-calorie meal increased the combined exposure (AUC_{0-inf}) of alectinib plus M4 by 3.1-fold (90% CI: 2.7, 3.6) following oral administration of a single 600 mg dose of ALECENSA.

Distribution

The apparent volume of distribution is 4,016 L for alectinib and 10,093 L for M4.

Alectinib and M4 are bound to human plasma proteins greater than 99%, independent of drug concentration.

Alectinib concentrations in the cerebrospinal fluid in patients with ALK-positive NSCLC approximate estimated alectinib free concentrations in the plasma.

In vitro studies suggest that alectinib is not a substrate of P-glycoprotein (P-gp), but M4 is a substrate of P-gp. Alectinib and M4 are not substrates of breast cancer resistance protein (BCRP), organic anion-transporting polypeptide (OATP) 1B1, or OATP1B3.

Elimination

The apparent clearance (CL/F) is 81.9 L/hour for alectinib and 217 L/hour for M4. The geometric mean elimination half-life is 33 hours for alectinib and 31 hours for M4 in patients with ALK-positive NSCLC.

Metabolism

Alectinib is metabolized by CYP3A4 to its major active metabolite M4. The geometric mean metabolite/parent exposure ratio at steady-state is 0.40. M4 is subsequently metabolized by CYP3A4. Alectinib and M4 were the main circulating moieties in plasma, constituting 76% of the total radioactivity.

Excretion

Ninety-eight percent of the radioactivity was excreted in feces following oral administration of a single radiolabeled dose of alectinib under fed conditions. Eighty-four percent of the dose was excreted in the feces as unchanged alectinib, and 6% of the dose was excreted as M4. Excretion of radioactivity in urine was less than 0.5% of administered radiolabeled dose of alectinib.

Specific Populations

Age (21 to 83 years), body weight (38 to 128 kg), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to ≤ 1.5 × ULN and AST any value), mild to moderate renal impairment (creatinine clearance 30 to 89 mL/min), race (White, Asian, and Other), and sex had no clinically meaningful effect on the systemic exposure of alectinib and M4. The pharmacokinetics of alectinib have not been studied in patients with severe renal impairment (creatinine clearance < 30 mL/min), or end-stage renal disease.

Hepatic Impairment: Following administration of a single oral dose of 300 mg ALECENSA, the geometric mean ratio [90% confidence interval] for the combined AUC_{inf} of alectinib and M4 in subjects with moderate hepatic impairment (Child-Pugh B) was 1.36 [0.947, 1.96] and in subjects with severe hepatic impairment (Child-Pugh C) was 1.76 [0.984, 3.15] as compared to that in subjects with normal hepatic function. The combined C_{max} of alectinib and M4 was comparable among the three groups. No dose adjustment is recommended for patients with mild or moderate hepatic impairment. The recommended dose of ALECENSA in patients with severe hepatic impairment is 450 mg orally twice daily *[see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]*.

Drug Interactions

Effect of Other Drugs on Alectinib

No clinically meaningful effect on the combined exposure of alectinib plus M4 was observed in clinical studies following co-administration of ALECENSA with a strong CYP3A inhibitor (posaconazole), a strong CYP3A inducer (rifampin), or an acid-reducing agent (esomeprazole).

Effect of Alectinib on Other Drugs

No clinically meaningful effect on the exposure of midazolam (sensitive CYP3A substrate) or repaglinide (sensitive CYP2C8 substrate) is expected following co-administration with ALECENSA.

In vitro studies suggest that alectinib and M4 do not inhibit CYP1A2, 2B6, 2C9, 2C19 or 2D6.

In vitro studies suggest that alectinib and M4 inhibit P-gp and BCRP. Alectinib did not inhibit OATP1B1, OATP1B3, OAT1, OAT3, or OCT2 transport activity in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with alectinib have not been conducted.

Alectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay, but was positive with an increased number of 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.

No studies in animals have been performed to evaluate the effect of alectinib on fertility. No adverse effects on male and female reproductive organs were observed in general toxicology studies conducted in rats and monkeys.

14 CLINICAL STUDIES

14.1 Adjuvant Treatment of Resected ALK-Positive NSCLC

The efficacy of ALECENSA for the adjuvant treatment of patients with ALK-positive NSCLC following complete tumor resection was evaluated in a global, randomized open-label clinical trial (ALINA: NCT03456076). Eligible patients were required to have resectable ALK-positive NSCLC, Stage IB (tumors ≥ 4 cm) – IIIA per the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) Staging System, 7th Edition. ALK rearrangements were identified by a locally performed FDA-approved ALK test or by a centrally performed VENTANA ALK (D5F3) CDx assay.

Randomization was stratified by race (Asian vs. other races) and stage of disease (IB vs. II vs. IIIA). Patients were randomized (1:1) to receive ALECENSA 600 mg orally twice daily or platinum-based chemotherapy following tumor resection. Treatment with ALECENSA continued 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 AUC 5 mg/mL/min or 6 mg/mL/min.

The major efficacy outcome measures were disease-free survival (DFS) in patients with stage II-IIIA NSCLC and DFS in patients with stage IB-IIIA NSCLC (intent-to-treat [ITT] population) as assessed by investigator. DFS was defined as the time from date of randomization 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. An additional efficacy outcome measure was overall survival (OS) in the ITT population.

A total of 257 patients were randomized to ALECENSA (N=130) or to chemotherapy (N=127). The median age was 56 years (range: 26 to 87), 24% were ≥ 65 years old; 52% were female; 56% were Asian, 42% were White, 0.4% were Black or African American, 2.3% were race unknown; 0.4% were Hispanic or Latino; 60% were never smokers; 53% had an ECOG PS of 0; 10% of patients had Stage IB, 35% had Stage II and 55% had Stage IIIA disease.

ALINA demonstrated a statistically significant improvement in DFS for patients treated with ALECENSA compared to patients treated with chemotherapy. OS data were not mature at the time of DFS analysis with 2.3% of deaths reported in the ITT population.

The efficacy results from ALINA are summarized in Table 10 and Figure 1.

Table 10: Investigator-Assessed DFS Results in ALINA

Efficacy Parameter	Stage II-IIIA Population		ITT Population	
	ALECENSA N=116	Chemotherapy N=115	ALECENSA N=130	Chemotherapy N=127
DFS events (%)	14 (12)	45 (39)	15 (12)	50 (39)
Disease recurrence (%)	14 (12)	44 (38)	15 (12)	49 (38)
Death	0	1 (0.9)	0	1 (0.8)
Median DFS, months (95% CI)[a]	NR (NE, NE)	44.4 (27.8, NE)	NR (NE, NE)	41.3 (28.5, NE)
Hazard Ratio (95% CI)[b]	0.24 (0.13, 0.45)		0.24 (0.13, 0.43)	
p-value[c]	<0.0001		<0.0001	

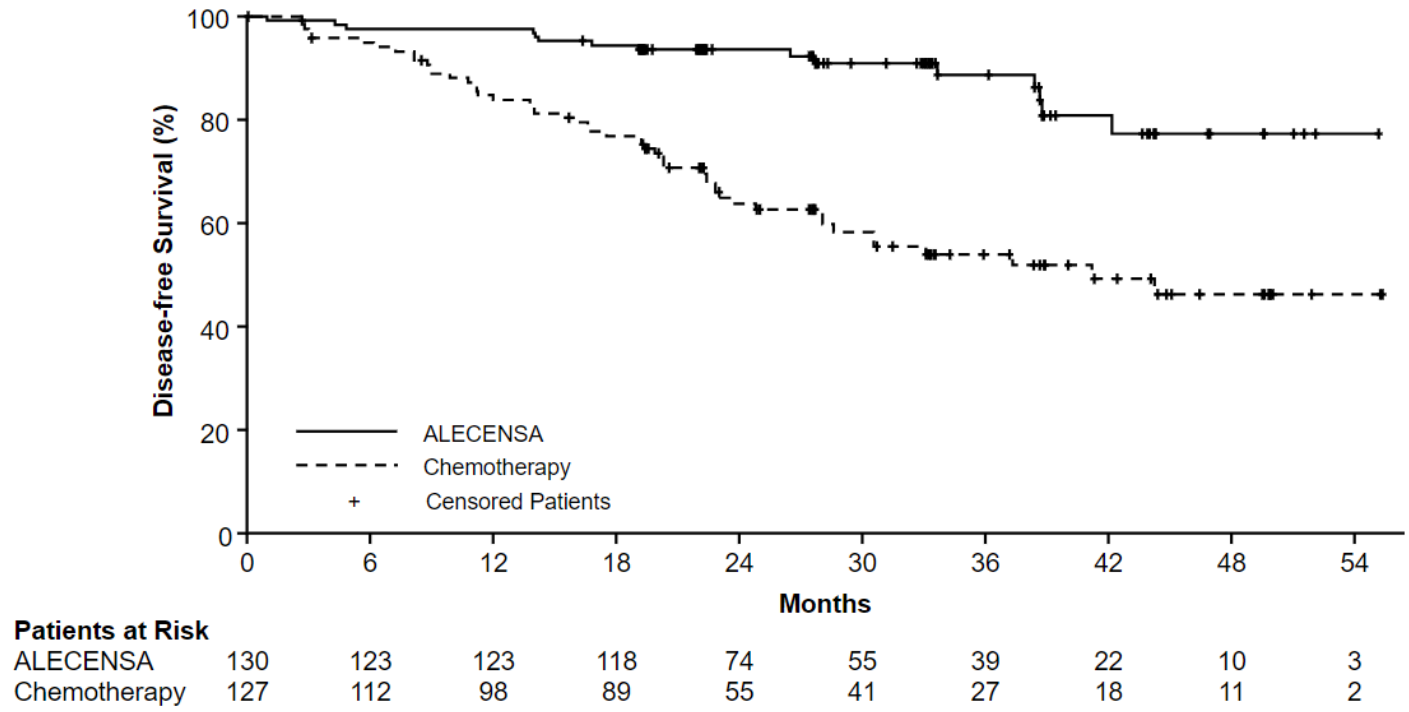
DFS = Disease-Free Survival; ITT = Intent-to-Treat; CI = Confidence Interval; NR = Not Reached; NE = Not Estimable.

[a] Kaplan-Meier method.

[b] Stratified Cox model, stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT.

[c] Stratified log-rank test stratified by race (Asian vs. other races) in Stage II-IIIA and stratified by race (Asian vs. other races) and tumor stage (Stage IB vs. II vs. IIIA) in ITT.

Figure 1: Kaplan-Meier Curves of Investigator-Assessed DFS (ITT Population) in ALINA



In an exploratory analysis of site(s) of relapse, the proportion of patients with brain involvement at the time of disease recurrence was 4 patients (3.1%) in the ALECENSA arm and 14 patients (11%) in the chemotherapy arm.

14.2 Treatment of Metastatic ALK-Positive NSCLC

Previously Untreated Metastatic ALK-Positive NSCLC

The efficacy of ALECENSA for the treatment of patients with ALK-positive NSCLC who had not received prior systemic therapy for metastatic disease was established in an open-label, randomized, active-controlled, multicenter study (ALEX: NCT02075840). Patients were required to have an ECOG performance status of 0-2 and ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx assay. Neurologically stable patients with treated or untreated central nervous system (CNS) metastases, including leptomeningeal metastases, were eligible; patients with neurologic signs and symptoms due to CNS metastases were required to have completed whole brain radiation or gamma knife irradiation at least 14 days prior to enrollment and be clinically stable. Patients with a baseline QTc > 470 ms were ineligible.

Patients were randomized 1:1 to receive ALECENSA 600 mg orally twice daily or crizotinib 250 mg orally twice daily. Randomization was stratified by ECOG performance status (0/1 vs. 2), race (Asian vs. other races), and the presence or absence of CNS metastases at baseline. Treatment on both arms was continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival (PFS) as determined by investigator assessment according to RECIST v1.1. Additional efficacy outcome measures were PFS as determined by independent review committee (IRC), time to CNS progression by IRC based on RECIST v1.1, objective response rate (ORR) and duration of response (DOR), and OS. Additional exploratory outcome measures were CNS objective response rate (CNS-ORR) and CNS duration of response (CNS-DOR) by IRC in patients with CNS metastases at baseline.

A total of 303 patients were randomized to ALECENSA (n=152) or crizotinib (n=151). The demographic characteristics of the study population were 56% female, median age 56 years (range: 18 to 91 years), 50% White, 46% Asian, 1% Black, and 3% other races. The majority of patients had adenocarcinoma (92%) and never smoked (63%). CNS metastases were present in 40% (n=122) of patients: of these, 43 patients had measurable CNS lesions as determined by an IRC. The ALEX study demonstrated a significant improvement in PFS. The time to cause-specific CNS progression as assessed by IRC was also significantly improved; there was a lower incidence of progression in the CNS as the first site of disease progression, alone or with concurrent systemic progression, in the ALECENSA arm (12%) as compared to the crizotinib arm (45%). Efficacy results from ALEX are summarized in Table 11 and Figure 2.

Table 11: Efficacy Results in ALEX per IRC Assessment

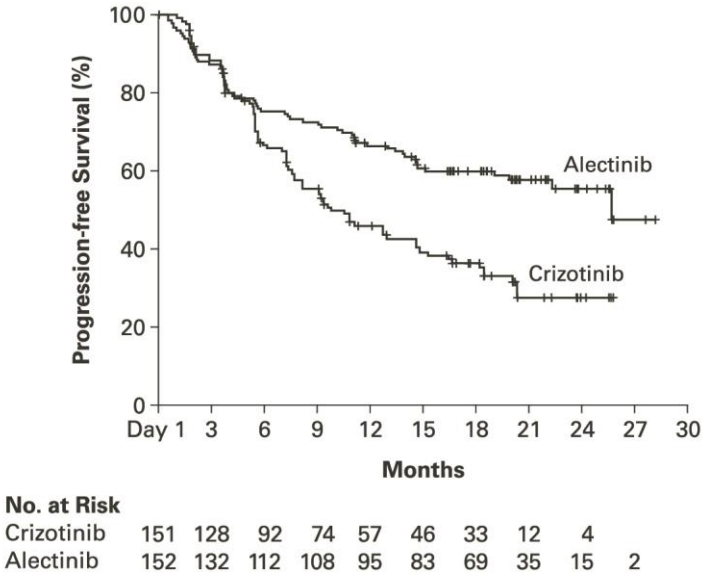
	ALECENSA N=152	**Crizotinib N=151**
Progression-Free Survival		
Number of events (%)	63 (41%)	92 (61%)
Progressive disease (%)	51 (34%)	82 (54%)
Death (%)	12 (8%)	10 (7%)
Median in months (95% CI)	25.7 (19.9, NE)	10.4 (7.7, 14.6)
Hazard ratio (95% CI) [a]	0.53 (0.38, 0.73)	
P-value [b]	< 0.0001	
Overall Response Rate		
Overall response rate, % (95% CI) [c]	79% (72, 85)	72% (64, 79)
P-value [d]	0.1652	
Complete response, %	13%	6%
Partial response, %	66%	66%
Duration of Response		
Number of responders	n=120	n=109
Response duration ≥6 months	82%	57%
Response duration ≥12 months	64%	36%
Response duration ≥18 months	37%	14%

CNS: central nervous system, ORR: overall response rate, IRC: independent review committee, CI: confidence interval, NE: not estimable.

[a, b, d] Stratified by race (Asian vs. other races) and CNS metastases at baseline (yes vs. no) for Cox model, log-rank test and Cochran Mantel-Haenszel test, respectively.

[c] Clopper and Pearson exact binomial 95% confidence interval.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival (IRC) in ALEX



Results for PFS as determined by investigator assessment (HR=0.48 [95% CI: 0.35-0.66], stratified log-rank p<0.0001) were similar to that observed by IRC. At the data cutoff point overall survival data was not mature.

The results of prespecified exploratory analyses of CNS response rate in patients with measurable CNS lesions at baseline are summarized in Table 12.

Table 12: IRC-Assessed CNS Responses in Patients with Measurable CNS Lesions at Baseline in ALEX

	ALECENSA	**Crizotinib**
CNS Tumor Response Assessment	N = 21	N = 22
CNS Objective Response Rate, % (95% CI[a])	81% (58, 95)	50% (28,72)
Complete Response	38%	5%
Duration of CNS Response		
Number of responders	17	11
CNS response duration ≥ 12 months	59%	36%

IRC: Independent Review Committee; CI: Confidence Interval; NE: Not Estimable
[a] Clopper and Pearson exact binomial 95% confidence interval

Metastatic ALK-Positive NSCLC Previously Treated with Crizotinib

The safety and efficacy of ALECENSA were established in two single-arm, multicenter clinical trials: NP28761 (NCT01588028) and NP28673 (NCT01801111). Patients with locally advanced or metastatic ALK-positive NSCLC, who have progressed on crizotinib, with documented ALK-positive NSCLC based on an FDA-approved test, and ECOG PS of 0-2 were enrolled in both studies. Eligibility criteria permitted enrollment of patients with prior chemotherapy and prior CNS radiotherapy provided that CNS metastases were stable for at least two weeks. All patients received ALECENSA 600 mg orally twice daily. The major efficacy outcome measure in both studies was objective response rate (ORR) according to Response Evaluation Criteria in Solid

Tumors (RECIST v1.1) as evaluated per Independent Review Committee (IRC). Additional outcome measures as evaluated by the IRC included duration of response (DOR), CNS ORR, and CNS DOR.

NP28761 was conducted in North America and enrolled 87 patients. Baseline demographic and disease characteristics in NP28761 were median age 54 years old (range 29 to 79, 18% 65 and over), 84% White and 8% Asian, 55% female, 35% ECOG PS 0 and 55% ECOG PS 1, 100% never or former smokers, 99% Stage IV, 94% adenocarcinoma, and 74% prior chemotherapy. The most common sites of extra-thoracic metastasis included 60% CNS (of whom 65% had received CNS radiation), 43% lymph nodes, 36% bone, and 34% liver.

NP28673 was conducted internationally and enrolled 138 patients. Baseline demographic and disease characteristics in NP28673 were median age 52 years old (range 22 to 79, 10% 65 and over), 67% White and 26% Asian, 56% female, 32% ECOG PS 0 and 59% ECOG PS 1, 98% never or former smokers, 99% Stage IV, 96% adenocarcinoma, and 80% prior chemotherapy. The most common sites of extra-thoracic metastasis included 61% CNS (of whom 73% had received CNS radiation), 51% bone, 38% lymph nodes, and 30% liver.

Efficacy results from NP28761 and NP28673 in all treated patients are summarized in Table 13. The median duration of follow-up on Study NP28761 was 4.8 months for both IRC and Investigator assessments and on Study NP28673, 10.9 months for IRC assessment and 7.0 months for Investigator assessment. All responses were partial responses.

Table 13: Efficacy Results in Studies NP28761 and NP28673

Efficacy Parameter	**NP28761 (N=87)**		**NP28673 (N=138)**	
	IRC* Assessment	**Investigator Assessment**	**IRC* Assessment**	**Investigator Assessment**
Objective Response Rate (95% CI)	38% (28; 49)	46% (35; 57)	44% (36; 53)	48% (39; 57)
Number of Responders	33	40	61	66
Duration of Response, median in months (95% CI)	7.5 (4.9, Not Estimable)	NE (4.9, Not Estimable)	11.2 (9.6, Not Estimable)	7.8 (7.4, 9.2)

* 18 patients in NP28761 and 16 patients in NP28673 did not have measurable disease at baseline as per IRC assessment and were classified as non-responders in the IRC analysis.

An assessment of ORR and duration of response for CNS metastases in the subgroup of 51 patients in NP28761 and NP28673 with baseline measurable lesions in the CNS according to RECIST v1.1 are summarized in Table 14. Thirty-five (69%) patients with measurable CNS lesions had received prior brain radiation, including 25 (49%) who completed radiation treatment at least 6 months before starting treatment with ALECENSA. Responses were observed irrespective of prior brain radiation status.

Table 14: CNS Objective Response in Patients with Measurable CNS Lesions in Studies NP28761 and NP28673

Efficacy Parameter	**N=51**
CNS Objective Response Rate (95% CI)	61% (46, 74)
Complete Response	18%
Partial Response	43%
CNS Duration of Response, median in months (95% CI)	9.1 (5.8, Not Estimable)

16 HOW SUPPLIED/STORAGE AND HANDLING

Hard capsules, white 150 mg capsules with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body, available in:

240 capsules per bottle: NDC 50242-130-01

Storage and stability: Do not store above 30°C (86°F). Store in the original container to protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Hepatotoxicity

Inform patients of the signs and symptoms of bilirubin and hepatic transaminase elevations. Advise patients to contact their healthcare provider immediately for signs or symptoms of bilirubin and hepatic transaminase elevations *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the risks of severe ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.2)]*.

Renal Impairment

Inform patients of the risk of severe and potentially fatal renal impairment. Advise patients to contact their healthcare provider for change in urine color, reduced urine output, or swelling in the legs and feet *[see Warnings and Precautions (5.3)]*.

Bradycardia

Inform patients that symptoms of bradycardia including dizziness, lightheadedness, and syncope can occur while taking ALECENSA. Advise patients to contact their healthcare provider to report these symptoms and to inform their healthcare provider about the use of any heart or blood pressure medications *[see Warnings and Precautions (5.4)]*.

Severe Myalgia/CPK Elevation

Inform patients of signs and symptoms of myalgia, including unexplained and/or persistent muscle pain, tenderness, or weakness. Advise patients to contact their healthcare provider immediately to report new or worsening symptoms of muscle pain or weakness *[see Warnings and Precautions (5.5)]*.

Hemolytic Anemia

Advise patients to contact their healthcare provider if they develop any signs or symptoms of hemolytic anemia *[see Warnings and Precautions (5.6)]*.

Photosensitivity

Inform patients of the signs and symptoms of photosensitivity. Advise patients to avoid prolonged sun exposure while taking ALECENSA and for at least 7 days after study drug discontinuation and to use proper protection from the sun. Advise patients to use a broad spectrum ultraviolet A (UVA)/ultraviolet B (UVB) sunscreen and lip balm (SPF ≥ 50) to help protect against potential sunburn *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

ALECENSA can cause fetal harm if taken during pregnancy. Advise a pregnant woman and females of reproductive potential of the potential risk to a fetus *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1, 8.3)]*.

Advise females of reproductive potential to use effective contraception during treatment with ALECENSA and for 5 weeks after the last dose of ALECENSA. Advise patients to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1, 8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ALECENSA and for 3 months after the last dose *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with ALECENSA and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Administration

Instruct patients to take ALECENSA twice a day. Advise patients to take ALECENSA with food and to swallow ALECENSA capsules whole *[see Dosage and Administration (2.2)]*.

Missed Dose

Advise patients that if a dose of ALECENSA is missed or if the patient vomits after taking a dose of ALECENSA, patients should be advised not to take an extra dose, but to take the next dose at the regular time *[see Dosage and Administration (2.2)]*.

Distributed by:
Genentech USA, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

ALECENSA® is a registered trademark of Chugai Pharmaceutical Co., Ltd., Tokyo, Japan
©2024 Genentech, Inc. All rights reserved.

PATIENT INFORMATION

ALECENSA® (a-le-sen-sah)

(alectinib)

capsules

What is the most important information I should know about ALECENSA?

ALECENSA may cause serious side effects, including:

- **Liver problems (hepatotoxicity).** Liver problems are common with ALECENSA and can be severe. Your healthcare provider will do blood tests at least every 2 weeks for the first 3 months, and then 1 time each month and as needed during treatment with ALECENSA to check your liver function. **Tell your healthcare provider right away if you get any of the following signs and symptoms:**
  - feeling tired
  - feeling less hungry than usual
  - yellowing of your skin or the whites of your eyes
  - dark urine
  - itchy skin
  - nausea or vomiting
  - pain on the right side of your stomach area
  - bleeding or bruising more easily than normal
- **Lung problems.** ALECENSA may cause severe or life-threatening swelling (inflammation) of the lungs during treatment. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including trouble breathing, shortness of breath, cough, or fever.
- **Kidney problems.** ALECENSA may cause severe kidney problems that can lead to death. Tell your healthcare provider right away if you have a change in the amount or color of your urine, or if you get new or worsening swelling in your legs or feet.
- **Slow heartbeat (bradycardia).** ALECENSA may cause very slow heartbeats that can be severe. Your healthcare provider will check your heart rate and blood pressure during treatment with ALECENSA. Tell your healthcare provider right away if you feel dizzy, lightheaded, or if you faint during treatment with ALECENSA. Tell your healthcare provider if you take any heart or blood pressure medicines.
- **Severe muscle pain, tenderness, and weakness (myalgia).** Muscle problems are common with ALECENSA and can be severe. Your healthcare provider will do blood tests at least every 2 weeks for the first month and as needed during treatment with ALECENSA. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Breakdown of healthy red blood cells earlier than normal (hemolytic anemia).** Hemolytic anemia can happen in some people who take ALECENSA. If this happens, you may not have enough healthy red blood cells. Your healthcare provider may temporarily stop ALECENSA and do blood tests, if needed, to check for this problem. If you develop hemolytic anemia, your healthcare provider may either restart you on ALECENSA at a lower dose when the hemolytic anemia goes away, or may stop your treatment with ALECENSA. Tell your healthcare provider right away if you experience yellow skin (jaundice), weakness or dizziness, or shortness of breath.

See "What are the possible side effects of ALECENSA?" for more information about side effects.

What is ALECENSA?

ALECENSA is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that is caused by an abnormal anaplastic lymphoma kinase (ALK) gene:

- to help prevent your lung cancer from coming back after your tumor has been removed by surgery (adjuvant), **or**
- as treatment when your lung cancer has spread to other parts of your body (metastatic).

Your healthcare provider will perform a test to make sure that ALECENSA is right for you.

It is not known if ALECENSA is safe and effective in children.

Before you take ALECENSA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have lung or breathing problems
- have a slow heartbeat
- are pregnant or plan to become pregnant. ALECENSA can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will do a test to see if you are pregnant before starting treatment with ALECENSA.
  - You should use effective birth control (contraception) during treatment with ALECENSA and for 5 weeks after the last dose of ALECENSA.
  - Tell your healthcare provider right away if you become pregnant during treatment with ALECENSA or think you may be pregnant.

  Males who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with ALECENSA and for 3 months after the last dose of ALECENSA.
- are breastfeeding or plan to breastfeed. It is not known if ALECENSA passes into your breast milk. Do not breastfeed during treatment with ALECENSA and for 1 week after the last dose of ALECENSA. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, or herbal supplements.

How should I take ALECENSA?

- Take ALECENSA exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking ALECENSA unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with ALECENSA if you have side effects.
- Take ALECENSA 2 times a day.
- Take ALECENSA with food.
- Swallow ALECENSA capsules whole. Do not open or dissolve the capsule contents.
- If you miss a dose of ALECENSA, do not take the missed dose. Take your next dose at your regular time.
- If you vomit after taking a dose of ALECENSA, do not take an extra dose. Take your next dose at your regular time.

What should I avoid while taking ALECENSA?

Avoid spending time in the sunlight during treatment with ALECENSA and for 7 days after the last dose of ALECENSA. Your skin may be sensitive to the sun (photosensitivity) and you may burn more easily and get severe sunburns. Use sun protecting measures, such as sunscreen and lip balm with an SPF 50 or greater to help protect against sunburn.

What are the possible side effects of ALECENSA?

ALECENSA may cause serious side effects, including:

- **See "What is the most important information I should know about ALECENSA?"**

The most common side effects of ALECENSA include:

- constipation
- tiredness
- swelling in your hands, feet, ankles, face and eyelids
- rash
- cough

These are not all of the possible side effects of ALECENSA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ALECENSA?

- Do not store ALECENSA at temperatures above 86°F (30°C).
- Store ALECENSA capsules in the original container.
- Keep ALECENSA capsules dry and away from light.

Keep ALECENSA and all medicines out of the reach of children.

General information about the safe and effective use of ALECENSA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ALECENSA for a condition for which it was not prescribed. Do not give ALECENSA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ALECENSA that is written for health professionals.

What are the ingredients in ALECENSA?

Active ingredient: alectinib

Inactive ingredients: lactose monohydrate, hydroxypropylcellulose, sodium lauryl sulfate, magnesium stearate and carboxymethylcellulose calcium. Capsule shell contains: hypromellose, carrageenan, potassium chloride, titanium dioxide, corn starch, and carnauba wax. Printing ink contains: red iron oxide (E172), yellow iron oxide (E172), FD&C Blue No. 2 aluminum lake (E132), carnauba wax, white shellac, and glyceryl monooleate.

Distributed by: Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

ALECENSA® is a registered trademark of Chugai Pharmaceutical Co., Ltd., Tokyo, Japan

© 2024 Genentech, Inc.

For more information, go to www.ALECENSA.com or call 1-800-253-2367.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 04/2024

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 hard capsule of 19.2 mm length, with "ALE" printed in black ink on the cap and "150 mg" printed in black ink on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adjuvant treatment of resected non-small cell lung cancer (NSCLC)

Alecensa as monotherapy is indicated as adjuvant treatment following complete tumour resection for adult patients with ALK-positive NSCLC at high risk of recurrence (see section 5.1 for selection criteria).

Treatment of advanced NSCLC

Alecensa as monotherapy is indicated for the first-line treatment of adult patients with ALK-positive advanced NSCLC.

Alecensa as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib.

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 > 5 times ULN with total bilirubin ≤ 2 times ULN	Temporarily withhold until recovery to baseline or ≤ 3 times ULN, then resume at reduced dose (see Table 1).
ALT or AST elevation of > 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.

CTCAE grade	Alecensa treatment
	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
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		

System organ class ADRs (MedDRA)	**Alecensa** **N=533**	
	Frequency category (all grades)	**Frequency category (grades 3-4)**
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

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.

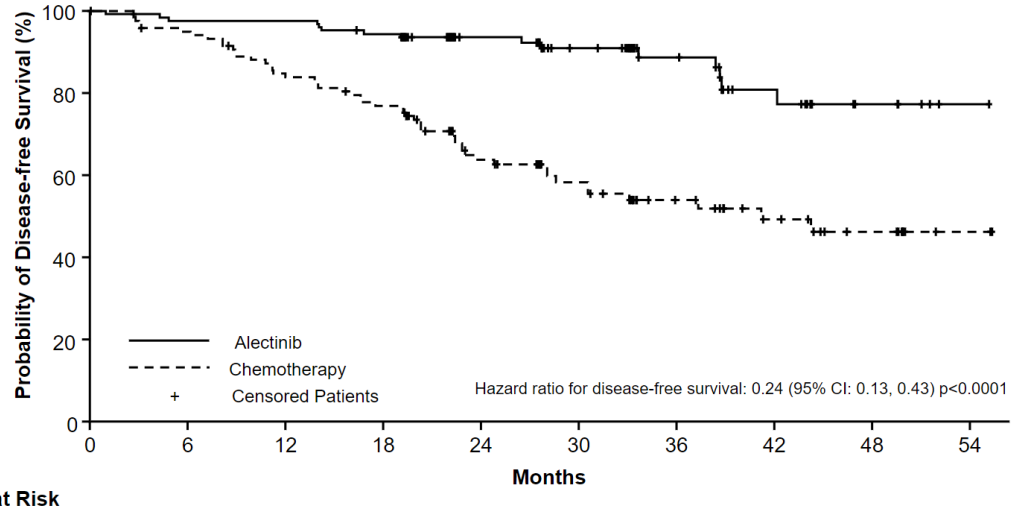
The DFS efficacy results are summarised in Table 4 and Figure 1.

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

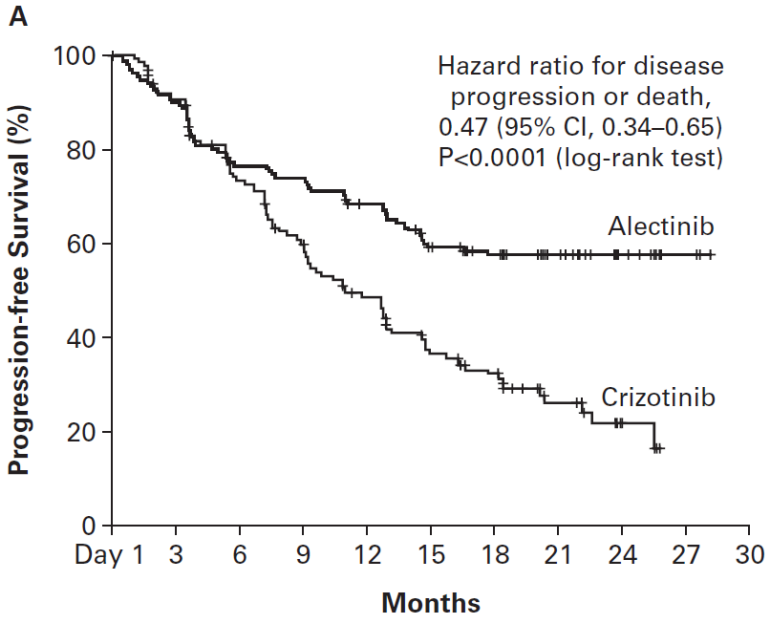
** Competing risk analysis of CNS progression, systemic progression and death as competing events

*** 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

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Alecensa in all subsets of the paediatric population in lung carcinoma (small cell and non-small cell carcinoma) (see section 4.2 for information on paediatric use).

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

Capsule content
Lactose monohydrate
Hydroxypropylcellulose
Sodium laurilsulfate
Magnesium stearate
Carmellose calcium

Capsule shell
Hypromellose
Carrageenan
Potassium chloride
Titanium dioxide (E171)
Maize starch
Carnauba wax

Printing ink
Red iron oxide (E172)
Yellow iron oxide (E172)
Indigo carmine aluminum lake (E132)
Carnauba wax
White shellac
Glyceryl monooleate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Blisters
Store in the original package in order to protect from moisture.

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

6.5 Nature and contents of container

Aluminium/aluminium (PA/Alu/PVC/Alu) blisters containing 8 hard capsules.
Pack size: 224 (4 packs of 56) hard capsules.

HDPE bottle with a child-resistant closure and an integrated desiccant.
Pack size: 240 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 Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/001
EU/1/16/1169/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 February 2017
Date of latest renewal: 15 July 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release
Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreeed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due Date
Post Authorisation Efficacy Study (PAES): In order to further evaluate the efficacy of Alecensa as monotherapy as adjuvant treatment following complete tumour resection for adult patients with Stage IB (≥ 4 cm) - IIIA ALK-postitive NSCLC, the MAH should submit the following results from the BO40336 study:	
• Updated descriptive DFS and descriptive OS results	Q3 2025
• 5-year survival follow up results	Q3 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

224 (4 packs of 56) hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

alecensa

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON FOR BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

56 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

alecensa

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

240 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

alecensa

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Alecensa 150 mg hard capsules
alectinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains lactose and sodium. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

240 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package and keep the bottle tightly closed in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1169/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Alecensa 150 mg hard capsules
alectinib

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alecensa is and what it is used for
2. What you need to know before you take Alecensa
3. How to take Alecensa
4. Possible side effects
5. How to store Alecensa
6. Contents of the pack and other information

1. What Alecensa is and what it is used for

What Alecensa is

Alecensa is a cancer medicine that contains the active substance alectinib.

What Alecensa is used for

Alecensa is used to treat adults with a type of lung cancer called ‘non-small cell lung cancer’ (‘NSCLC’) that is ‘ALK-positive’ - this means your cancer cells have a fault in a gene that makes an enzyme called ALK (‘anaplastic lymphoma kinase’) fusion, see ‘How Alecensa works’, below.

Alecensa can be prescribed to you:
- after removal of your cancer as a post-surgical (adjuvant) treatment, or
- as the first treatment of your lung cancer that has spread to other parts of the body (advanced), or if you have been previously treated with a medicine containing ‘crizotinib’.

How Alecensa works

Alecensa blocks the action of an enzyme called ‘ALK tyrosine kinase’. Abnormal forms of this enzyme (due to fault in the gene that makes it) help encourage cancer cell growth. Alecensa may slow down or stop the growth of your cancer and may prevent the tumour from coming back after removal by surgery. It may also help to shrink your cancer.

If you have any questions about how Alecensa works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Alecensa

Do not take Alecensa

- if you are allergic to alectinib or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor, pharmacist or nurse before taking Alecensa.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Alecensa:
- if you have ever had stomach or intestine problems as holes (perforation), or if you have conditions causing inflammation inside the abdomen (diverticulitis), or if you have spread of cancer inside the abdomen (metastasis). It is possible that Alecensa may increase the risk of developing holes in the wall of your gut.
- if you have an inherited problem called 'galactose intolerance', 'congenital lactase deficiency' or 'glucose-galactose malabsorption'.

If you are not sure, talk to your doctor, pharmacist or nurse before taking Alecensa.

Talk to your doctor right away after having taken Alecensa:
- if you are experiencing severe stomach or abdominal pain, fever, chills, sickness, vomiting, or abdominal rigidity or bloating, as these could be symptoms of a hole in the wall of your gut.

Alecensa can cause side effects that you need to tell your doctor about straight away. These include:
- liver injury (hepatotoxicity). Your doctor will take blood tests before you start treatment, then every 2 weeks for the first 3 months of your treatment and then less often. This is to check you do not have any liver problems while taking Alecensa. Tell your doctor straight away if you get any of the following signs: yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling less hungry than usual, nausea or vomiting, feeling tired, bleeding or bruising more easily than normal.
- slow heart beat (bradycardia).
- lung inflammation (pneumonitis). Alecensa may cause severe or life-threatening swelling (inflammation) of the lungs during treatment. The signs may be similar to those from your lung cancer. Tell your doctor straight away if you have any new or worsening signs including difficulty in breathing, shortness of breath, or cough with or without mucus, or fever.
- severe muscle pain, tenderness, and weakness (myalgia). Your doctor will do blood tests at least every 2 weeks for the first month and as needed during treatment with Alecensa. Tell your doctor straight away if you get new or worsening signs of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- abnormal breakdown of red blood cells (haemolytic anaemia). Tell your doctor straight away if you feel tired, weak or short of breath.

Look out for these while you are taking Alecensa. See 'Side effects' in section 4 for more information.

Sensitivity to sunlight

Do not expose yourself to the sun for any long period of time while you are taking Alecensa and for 7 days after you stop. You need to apply sunscreen and lip balm with a sun protection factor (SPF) of 50 or higher to help prevent sunburn.

Tests and checks

When you take Alecensa your doctor will do blood tests before you start treatment, then every 2 weeks for the first 3 months of your treatment and then less often. This is to check you do not have any liver or muscle problems while taking Alecensa.

Children and adolescents

Alecensa has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and Alecensa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, and herbal medicines. This is because Alecensa can affect the way some other medicines work. Also some other medicines can affect the way Alecensa works.

In particular tell your doctor or pharmacist if you are taking any of the following medicines:
- digoxin, a medicine used to treat heart problems
- dabigatran etexilate, a medicine used to treat blood clots
- methotrexate, a medicine used to treat severe joint inflammation, cancer and the skin disease psoriasis
- nilotinib, a medicine used to treat certain types of cancer
- lapatinib, a medicine used to treat certain types of breast cancer
- mitoxantrone, a medicine used to treat certain types of cancer or multiple sclerosis (a disease that affects the central nervous system which damages the coating that protects the nerves)
- everolimus, a medicine used to treat certain types of cancer or used to prevent the body's immune system from rejecting an organ transplant
- sirolimus, a medicine used to prevent the body's immune system from rejecting an organ transplant
- topotecan, a medicine used to treat certain types of cancer
- medicines used to treat acquired immunodeficiency syndrome/human immunodeficiency virus (AIDS/HIV) (e.g. ritonavir, saquinavir)
- medicines used to treat infections. These include medicines that treat fungal infections (antifungals such as ketoconazole, itraconazole, voriconazole, posaconazole) and medicines that treat certain types of bacterial infection (antibiotics such as telithromycin)
- St. John's Wort, a herbal medicine used to treat depression
- medicines used to stop seizures or fits (anti-epileptics such as phenytoin, carbamazepine, or phenobarbital)
- medicines used to treat tuberculosis (e.g. rifampicin, rifabutin)
- nefazodone, a medicine used to treat depression

Oral contraceptives

If you take Alecensa whilst using oral contraceptives, the oral contraceptives may be less effective.

Alecensa with food and drink

Tell your doctor or pharmacist if you drink grapefruit juice or eat grapefruit or Seville oranges while on treatment with Alecensa as they may change the amount of Alecensa in your body.

Contraception, pregnancy, and breast-feeding - information for women

Contraception - information for women

- You should not become pregnant while taking this medicine. If you are able to become pregnant, you must use highly effective contraception while on treatment and for at least 3 months after stopping treatment. Talk to your doctor about the right methods of contraception for you and your partner. If you take Alecensa whilst using oral contraceptives, the oral contraceptives may be less effective.

Pregnancy

- Do not take Alecensa if you are pregnant. This is because it may harm your baby.
- If you become pregnant when taking the medicine or during the 3 months after taking your last dose, tell your doctor straight away.

Breast-feeding

- Do not breast-feed while taking this medicine. This is because it is not known if Alecensa can pass over into breast milk and could therefore harm your baby.

Driving and using machines

Take special care when driving and using machines as you may develop problems with vision or slowing of the heartbeat or low blood pressure that can lead to fainting or dizziness while you are taking Alecensa.

Alecensa contains lactose

Alecensa contains lactose (a type of sugar). If you have been told by your doctor that you cannot tolerate or digest some sugars, talk to your doctor before taking this medicine.

Alecensa contains sodium

This medicine contains 48 mg sodium (main component of cooking/table salt) per recommended daily dose (1200 mg). This is equivalent to 2.4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take Alecensa

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor, pharmacist or nurse if you are not sure.

How much to take

- The recommended dose is 4 capsules (600 mg) twice a day.
- This means you take a total of 8 capsules (1200 mg) each day.

If you have severe liver problems before starting your treatment with Alecensa:

- The recommended dose is 3 capsules (450 mg) twice a day.
- This means you take a total of 6 capsules (900 mg) each day.

Sometimes your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely if you feel unwell.

How to take

- Alecensa is taken by mouth. Swallow each capsule whole. Do not open or dissolve the capsules.
- You must take Alecensa with food.

If you vomit after taking Alecensa

If you vomit after taking a dose of Alecensa, do not take an extra dose, just take your next dose at the usual time.

If you take more Alecensa than you should

If you take more Alecensa than you should, talk to a doctor or go to hospital straight away. Take the medicine pack and this leaflet with you.

If you forget to take Alecensa

- If it is more than 6 hours until your next dose, take the missed dose as soon as you remember.
- If it is less than 6 hours until your next dose, skip the missed dose. Then take your next dose at the usual time.
- Do not take a double dose to make up for a missed dose.

If you stop taking Alecensa

Do not stop taking this medicine without talking to your doctor first. It is important to take Alecensa twice a day for as long as your doctor prescribes it for you.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine. Some side effects could be serious.

Tell your doctor straight away if you notice any of the following side effects. Your doctor may lower your dose, stop your treatment for a short time or stop your treatment completely:

- New or worsening signs including difficulty in breathing, shortness of breath, or cough with or without mucus, or fever - the signs may be similar to those from your lung cancer (potential signs of lung inflammation – pneumonitis). Alecensa can cause severe or life-threatening inflammation of the lungs during treatment.
- Yellowing of your skin or the whites of your eyes, pain on the right side of your stomach area, dark urine, itchy skin, feeling less hungry than usual, nausea or vomiting, feeling tired, bleeding or bruising more easily than normal (potential signs of liver problems)
- New or worsening signs of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness (potential signs of muscle problems).
- Fainting, dizziness and low blood pressure (potential signs of slow heart beat)
- Feeling tired, weak or short of breath (potential signs of an abnormal breakdown of red blood cells, known as haemolytic anaemia).

Other side effects

Tell your doctor, pharmacist or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):

- abnormal results of blood tests to check for liver problems (high levels of alanine aminotransferase, aspartate aminotransferase and bilirubin)

- abnormal results of blood tests to check for muscle damage (high level of creatine phosphokinase)
- abnormal results of blood tests to check for liver disease or bone disorders (high level of alkaline phosphatase)
- you may feel tired, weak or short of breath due to a reduction in the number of red blood cells, known as anaemia
- vomiting – if you vomit after taking a dose of Alecensa, do not take an extra dose, just take your next dose at the usual time
- constipation
- diarrhoea
- nausea
- rash
- swelling caused by fluid build-up in the body (oedema)
- weight gain

Common (may affect up to 1 in 10 people):
- abnormal results of blood tests to check kidney function (high level of creatinine)
- inflammation of the mucous membrane of the mouth
- sensitivity to sunlight – do not expose yourself to the sun for any long period of time while you are taking Alecensa and for 7 days after you stop. You need to apply sunscreen and lip balm with a Sun Protection Factor of 50 or higher to help prevent sunburn.
- alteration in sense of taste
- problem with your eyes including blurred vision, loss of sight, black dots or white spots in your vision, and seeing double
- increased levels of uric acid in the blood (hyperuricaemia)

Uncommon (may affect up to 1 in 100 people):
- kidney problems including rapid loss of kidney function (acute kidney injury)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Alecensa

- Keep this medicine out of the sight and reach of children.
- Do not take this medicine after the expiry date which is stated on the carton and either the blister or the bottle after EXP. The expiry date refers to the last day of that month.
- If Alecensa is packed in blisters, store in the original package in order to protect from moisture.
- If Alecensa is packed in bottles, store in the original package and keep the bottle tightly closed to protect from moisture.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alecensa contains

- The active substance is alectinib. Each hard capsule contains alectinib hydrochloride equivalent to 150 mg alectinib.
- The other ingredients are:
    - *Capsule content:* lactose monohydrate (see section 2 'Alecensa contains lactose'), hydroxypropylcellulose, sodium laurilsulfate (see section 2 'Alecensa contains sodium'), magnesium stearate and carmellose calcium
    - *Capsule shell:* hypromellose, carrageenan, potassium chloride, titanium dioxide (E171), maize starch and carnauba wax
    - *Printing ink:* red iron oxide (E172), yellow iron oxide (E172), indigo carmine aluminium lake (E132), carnauba wax, white shellac and glyceryl monooleate.

What Alecensa looks like and contents of the pack

Alecensa hard capsules are white, with 'ALE' printed in black ink on the cap and '150 mg' printed in black ink on the body.

The capsules are provided in blisters and are available in cartons containing 224 hard capsules (4 packs of 56). The capsules are also available in plastic bottles containing 240 hard capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

Manufacturer

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
N.V. Roche S.A.
Tél/Tel: +32 (0) 2 525 82 11

България
Рош България ЕООД
Тел: +359 2 474 5444

Česká republika
Roche s. r. o.
Tel: +420 - 2 20382111

Lietuva
UAB "Roche Lietuva"
Tel: +370 5 2546799

Luxembourg/Luxemburg
(Voir/siehe Belgique/Belgien)

Magyarország
Roche (Magyarország) Kft.
Tel: +36 - 1 279 4500

Danmark
Roche Pharmaceuticals A/S
Tlf: +45 - 36 39 99 99

Deutschland
Roche Pharma AG
Tel: +49 (0) 7624 140

Eesti
Roche Eesti OÜ
Tel: + 372 - 6 177 380

Ελλάδα
Roche (Hellas) A.E.
Τηλ: +30 210 61 66 100

España
Roche Farma S.A.
Tel: +34 - 91 324 81 00

France
Roche
Tél: +33 (0) 1 47 61 40 00

Hrvatska
Roche d.o.o.
Tel: +385 1 4722 333

Ireland
Roche Products (Ireland) Ltd.
Tel: +353 (0) 1 469 0700

Ísland
Roche Pharmaceuticals A/S
c/o Icepharma hf
Sími: +354 540 8000

Italia
Roche S.p.A.
Tel: +39 - 039 2471

Κύπρος
Γ.Α.Σταμάτης & Σια Λτδ.
Τηλ: +357 - 22 76 62 76

Latvija
Roche Latvija SIA
Tel: +371 - 6 7039831

Malta
(See Ireland)

Nederland
Roche Nederland B.V.
Tel: +31 (0) 348 438050

Norge
Roche Norge AS
Tlf: +47 - 22 78 90 00

Österreich
Roche Austria GmbH
Tel: +43 (0) 1 27739

Polska
Roche Polska Sp.z o.o.
Tel: +48 - 22 345 18 88

Portugal
Roche Farmacêutica Química, Lda
Tel: +351 - 21 425 70 00

România
Roche România S.R.L.
Tel: +40 21 206 47 01

Slovenija
Roche farmacevtska družba d.o.o.
Tel: +386 - 1 360 26 00

Slovenská republika
Roche Slovensko, s.r.o.
Tel: +421 - 2 52638201

Suomi/Finland
Roche Oy
Puh/Tel: +358 (0) 10 554 500

Sverige
Roche AB
Tel: +46 (0) 8 726 1200

United Kingdom (Northern Ireland)
Roche Products (Ireland) Ltd.
Tel: +44 (0) 1707 366000

This leaflet was last revised in {**MM/YYYY**}.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web-site: https://www.ema.europa.eu.

Annex IV

Conclusions on the request for one-year marketing protection presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.

CORE DATA SHEET

ALECENSA, ALECENSARO

Alectinib

