Isolated Bilirubin Elevation Associated with Alecensa

This article responds to your request for information on Alecensa® (alectinib) and the management of isolated bilirubin elevations.

In brief

- Bilirubin elevations associated to Alecensa is a very common adverse drug reaction and should be closely monitored as biomarker of hepatotoxicity.
- Cases of isolated bilirubin elevations have been reported.
- Haemolytic anemia has been reported as ADR associated to Alecensa and could lead to isolated bilirubin elevations.
- FDA has established recommendations for management of isolated bilirubin elevations
- Refer to the local Alecensa label for information on the management of Alecensa related adverse events. Any deviation from this information is considered off-label and any treatment decisions based on such deviations are the full responsibility of the prescribing physician.

Abbreviations

CTCAE = NCI Common Terminology Criteria for Adverse Events
ALT = alanine aminotransferase
ADR= adverse drug reaction
AST = aspartate aminotransferase
ULN= upper limit of normal

Bilirubin elevations associated with Alecensa

Incidence of bilirubin elevations

Bilirubin elevations are considered a very common adverse drug reaction (ADR) associated with Alecensa,and cases include

- blood bilirubin increases
- hyperbilirubinaemia
- bilirubin conjugated increases and
- blood bilirubin unconjugated increases.

Bilirubin elevations were reported in 21% of Alecensa patients across clinical trials[1](NP28761[2], NP28673[3], BO28984[4]; n=405).

Monitoring bilirubin elevations

Label recommendations regarding bilirubin elevations associated with Alecensa are related to the management of hepatotoxicity. Table 1 shows recommendations for monitoring liver function during treatment with Alecensa, please refer to your local product label for further information.[5]

Table 1: Monitoring of liver function during treatment with Alecensa

The first 3 months...	Thereafter...
Monitor ALT, AST, and total bilirubin at baseline and then every 2 weeks.	Monitor periodically, since events may occur later than 3 months, with more frequent testing in patients who develop aminotransferase and bilirubin elevations.

Isolated bilirubin elevation associated with Alecensa

Incidence of isolated bilirubin elevations

Cases of bilirubin elevations without concurrent elevation of liver enzymes have been reported in the clinical practice[6,7].

Causes of isolated bilirubin elevations

There are multiple causative factors of isolated bilirubin elevation and a differential diagnosis should be performed.

Moreover, please be aware that haemolytic anemia is considered as an adverse drug reaction associated with Alecensa. Cases of haemolytic anemia have been reported in clinicals trials and post-marketing setting.[5,7] Refer to your local label for more information on haemolytic anemia associated to Alecensa.

Management of isolated bilirubin elevation

Please refer to your local Alecensa label for further information.

There is no guidance regarding the management of patients who experience isolated bilirubin elevations in the EMA label. The dose modification recommendations only cover total bilirubin elevations with concurrent elevations of ALT and AST. The general guidance in case of severe adverse events is to withhold Alecensa and resume at a reduced dose or permanently discontinue.[1]

However, the FDA label does provide recommendations for isolated total bilirubin elevations as described in Table 2.

Table 2. Dose modification recommendations for isolated bilirubin elevations with Alecensa treatment from the FDA label[8]

If...	then...

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

References

1. Alecensa Summary of Product Characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/alecensa-epar-product-information_en.pdf. Accessed on July 12, 2023.

2. Clinicaltrials.gov : A Study of Alectinib (CH5424802/RO5424802) in Participants With Anaplastic Lymphoma Kinase (ALK)-Rearranged Non-Small Cell Lung Cancer (NSCLC). Available at https://classic.clinicaltrials.gov/ct2/show/NCT01871805. Accessed on July 12, 2023.

3. Clinicaltrials.gov : A Study of Alectinib (RO5424802) in Participants With Non-Small Cell Lung Cancer Who Have Anaplastic Lymphoma Kinase (ALK) Mutation and Failed Crizotinib Treatment. Available at https://classic.clinicaltrials.gov/ct2/show/NCT01801111. Accessed on July 12, 2023.

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5. Roche Internal Regulatory Report, accessed on 12-Jul-2023.

6. Roche Internal Safety Report, accessed on 24-Aug-2023.

7. Roche Internal Safety Report, accessed on 24-Aug-2023.

8. FDA Alecensa Highlights of Prescribing Information. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208434s010lbl.pdf. Accessed on July 12, 2023.