Direct Healthcare Professional Communication
Columvi® (Glofitamab): New important identified risk of Neurologic Toxicity including Immune Effector Cell Associated Neurotoxicity (ICANS) with associated risk minimization measures

Columvi 2.5 mg concentrate for solution for infusion
Columvi 10 mg concentrate for solution for infusion

Jul 2024

צוות רפואי יקר,

חברת רוש פרמצבטיקה (ישראל) בע"מ, בשיתוף משרד הבריאות, מעוניינת להביא לידיעתך את המידע הבא הנוגע לתרופה Columvi:

Columvi (Glofitamab) הוא נוגדן בי-ספציפי (T-cell-engaging bispecific antibody) המיובא תחת תקנה 29 ונרשם לטיפול ב-

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B cell lymphoma, after two or more lines of systemic therapy.

להלן עיקרי הדברים:

- רעילות נוירולוגית כולל ICANS (Immune Effector Cell Associated Neurotoxicity), ובכללה תגובות חמורות ומוות, דווחה במטופלים ב-Columvi ונחשבת כסיכון מזוהה של התכשיר, בדומה לתכשירים אחרים מקבוצה זו (class effect).
- במחקר הקליני (NP30179) השכיחות הכוללת של רעילות נוירולוגית היתה 40% (בדרגה 3 ומעלה – 2.1%), כאשר תופעות הלוואי השכיחות ביותר היו כאבי ראש, נוירופתיה פריפרית, סחרחורת, שינויים במצב המנטלי וחרדה.
  השכיחות של ICANS היתה 4.8%, כאשר מרבית המקרים היו בדרגת חומרה 1 והתרחשו במהלך המחזור הראשון של Columvi. דווח מקרה אחד של ICANS בדרגה 5.
- יש לנטר את כל המטופלים לסימנים ותסמינים של רעילות נוירולוגית כולל ICANS לאחר מתן Columvi. תסמיני ICANS יכולים לכלול ישנוניות, פרכוסים, הפרעה קוגנטיבית, בלבול, דליריום וחוסר התמצאות במרחב.
- במקרה של הופעת תסמיני ICANS, ייתכן שיידרש טיפול בקורטיקוסטרואידים, תרופות נוגדות פרכוסים לא סדטיביות, טיפול תומך וייעוץ נוירולוגי. כתלות בדרגת החומרה של התופעה, ייתכן ויהיה צורך בהשהייה או בהפסקה של הטיפול (Table 1).
- העלון לרופא צפוי להתעדכן ויכלול מידע על שכיחות ומאפייני ICANS, הנחיות לניהול רעילות נוירולוגית כולל ICANS, והנחיות בנוגע לנהיגה ושימוש במכונות (יש להנחות מטופלים שחווים תסמינים של רעילות נוירולוגית להימנע מנהיגה או שימוש במכונות עד לחלוף הסימפטומים).
- יש ליידע את כל המטופלים החדשים ואת המטפלים שלהם אודות הסיכון ולהנחות אותם לפנות לקבלת טיפול רפואי באופן מיידי אם הם חווים סימנים או תסמינים של רעילות נוירולוגית. הכרטיס למטופל (המהווה חלק מהתוכנית למזעור סיכונים של התכשיר) יעודכן עם התסמינים הקשורים לסיכון זה.

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מידע נוסף:

COLUMVI (glofitamab) is a full-length, fully humanized, immunoglobulin G1 (IgG1), T-cell-engaging bispecific antibody (TCB) indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B cell lymphoma, after two or more lines of systemic therapy. COLUMVI must be administered as an intravenous infusion according to the dose step-up schedule leading to the recommended dose of 30 mg, after completion of pre-treatment with obinutuzumab on Cycle 1 Day 1. Each cycle is 21 days.

Adverse events consistent with ICANS (Lee 2019) following COLUMVI administration have been reported in a range of 0.4% in the post marketing setting to 8.1% across clinical trials. Based on the review of the available data, class effect of same-in-class drugs, the current evidence is sufficient to establish a causal association between glofitamab treatment and ICANS and its related events. Considering the class effect and labels of other bispecifics antibodies/cellular therapies, neurologic toxicity including ICANS is considered an appropriate description of this new important identified risk.

As the data from clinical Study NP30179 was used for the initial marketing authorization application, Roche is providing the following guidance and information relating to this risk and will be updating the prescribing information accordingly for patients who received at least one dose of COLUMVI (n=145):

- Neurologic toxicity including ICANS has been reported in patients receiving COLUMVI including serious and fatal reactions.
- The overall frequency of neurologic toxicity (including ICANS) was 40% and the most reported events are headache (10.3%), dizziness (5.5%), anxiety (4.1%). Additionally, Grade 3 or higher neurologic adverse reactions occurred in 2.1% of patients and included somnolence, delirium, and myelitis.
- ICANS events occurred in 4.8% patients treated with COLUMVI; the majority were Grade 1 events. 1 Grade 5 delirium was reported.
- ICANS may manifest as somnolence, seizures, cognitive disorder, confusional state, delirium and disorientation. The majority of cases of ICANS occurred during Cycle 1 of COLUMVI treatment, however, some events occurred at later cycles.
- All patients should be monitored for signs and symptoms of neurologic toxicity including immune effector cell associated neurotoxicity syndrome (ICANS) following COLUMVI administration.
- At the first signs or symptoms of ICANS, treatment with corticosteroids, non-sedating anti-seizure medicinal products, supportive therapies and neurologic consultation may be required.
- The prescribing information will also be updated to contain:
    - Dose interruption and withdrawal recommendations for COLUMVI treatment in the event of neurologic toxicity, including ICANS.
    - Updated guidance on the ability to drive will be provided (patients experiencing neurologic toxicity including ICANS should be advised not to drive or use machines until symptoms resolve).
    - ICANS and its frequency will be included in the adverse drug reaction table along with other existing neurologic toxicities.
    - The time to onset, duration and the frequency of ICANS that occurred concurrently with CRS.

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Roche is providing the following guidance relating to this risk in the Patient Card for COLUMVI and it will be updated accordingly:

- All new patients and their caregivers should be informed of risk of Neurologic toxicity including ICANS and must be instructed to seek immediate medical attention if they experience signs and symptoms of neurologic toxicity (Patient card to be also updated with these additional symptoms).

TABLE 1:

Recommended Dosage Modification for Neurologic Toxicity (Including ICANS)

Adverse Reaction	Severity[1,2]	Actions
Neurologic Toxicity[1] (including ICANS[2])	Grade 1	Continue Columvi and monitor neurologic toxicity symptoms. If ICANS, manage per current practice guidelines.
	Grade 2	Withhold Columvi until neurologic toxicity symptoms improve to Grade 1 or baseline.[3, 4] Provide supportive therapy, and consider neurologic evaluation. If ICANS, manage per current practice guidelines.
	Grade 3	Withhold Columvi until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days.[4, 5] For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing Columvi. Provide supportive therapy, and consider neurology evaluation. If ICANS, manage per current practice guidelines.
	Grade 4	Permanently discontinue Columvi. Provide supportive therapy, which may include intensive care, and consider neurology evaluation. If ICANS, manage per current practice guidelines.

[1] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
[2] Based on ASTCT 2019 grading for ICANS.
[3] Consider the type of neurologic toxicity before deciding to withhold Columvi.
[4] See *Dosage and Administration (2.2)* on restarting Columvi after dose delays.
[5] Evaluate benefit-risk before restarting Columvi.

Call for reporting

Healthcare professionals should report any adverse events, which are suspected to be associated with the use of Columvi, to the Israeli Ministry of Health by using an online form:
https://sideeffects.health.gov.il
Alternatively, it should be reported to Roche Israel drug safety department at 09-9737722 or israel.drugsafety@roche.com .

Company contact point

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Should you have any questions regarding the use of Columvi, please feel free to contact us at:

Roche Pharmaceuticals (Israel) Ltd.
email: Israel.drugsafety@roche.com
Tel: 09-9737777.

Yours sincerely,

Galia Tiram

Kolatkar Siyona

Galia Tiram, PhD
Medical Manager

Siyona Kolatkar
Qualified Person for Pharmacovigilance

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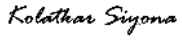
Kolatkar Siyona siyona.kolatkar@roche.com CFR Part 11 - Joint - Sub Account_310 Security Level: Email, Account Authentication (None)	 Signature Adoption: Pre-selected Style Using IP Address: 196.3.50.248	Sent: 7/24/2024 10:49:15 AM Viewed: 7/24/2024 10:49:23 AM Signed: 7/24/2024 10:49:44 AM
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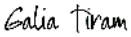
Galia Tiram galia.tiram@roche.com Medical Manager Galia tiram Security Level: Email, Account Authentication (None)	 Signature Adoption: Pre-selected Style Using IP Address: 196.3.50.247	Sent: 7/24/2024 10:49:46 AM Viewed: 7/24/2024 10:55:35 AM Signed: 7/24/2024 10:57:25 AM
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