Columvi®
Konzentrat zur Herstellung einer Infusionslösung, 1mg/1ml
Zul.-Nr. 68’297

Public Risk Management Plan (RMP) Summary

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of “Columvi” is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of “Columvi” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Roche Pharma (Schweiz) AG” is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Columvi”.

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR COLUMVI (GLOFITAMAB)

This is a summary of the Risk-management plan (RMP) for Columvi. The RMP details important risks of Columvi, how these risks can be minimized, and how more information will be obtained about Columvi's risks and uncertainties (missing information).

Columvi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Columvi should be used.

This summary of the RMP for Columvi should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Columvi's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Columvi as monotherapy is authorized for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, after two or more lines of systemic therapy (see SmPC for the full indication). It contains glofitamab as the active substance and is administered as an intravenous infusion.

Further information about the evaluation of Columvi's benefits can be found in Columvi's EPAR, including in its plain-language summary, available on the EMA webpage, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Columvi, together with measures to minimize such risks and the proposed studies for learning more about Columvi's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorized pack size-The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status-The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Columvi, these measures are supplemented with *additional risk-minimization measures* mentioned under relevant risks below.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR (Periodic Safety Update Report) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Columvi is not yet available, it is listed under "Missing Information" below.

II.A List of Important Risks and Missing Information

Important risks of Columvi are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Columvi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Cytokine release syndrome • Tumor Flare • Serious infections • Immune effector cell-associated neurotoxicity syndrome (ICANS)
Important potential risks	None
Missing information	• Long-term safety • Safety in patients with prior CAR-T therapy

II.B Summary of Important Risks

Important Identified Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	• Non-clinical studies, showing transient T-cell activation and cytokine release, primarily limited to the first dose • Phase I/II clinical trial data (Study NP30179) • Class effect: As observed with other CD3 engagers such as blinatumomab and CAR T-cell therapy, T-cell activation may lead to an excess of systemic cytokine release which may lead to serious and even fatal events
Risk factors and risk groups	The risk of CRS may be influenced by factors related to the type of therapy and treatment dose, the underlying disease (type, tumor burden, and tumor cell location [e.g., peripheral blood vs. bone marrow], patient characteristics (age, general health status, and comorbidity burden; basal inflammatory state), and degree of T-cell activation and expansion. Disease burden is among the most important predictors of severe CRS after CAR T-cell therapy and the bispecific T-cell engager blinatumomab.
Risk-minimization measures	**Routine risk-minimization measures:** SmPC section 4.2, 4.4 and 4.8 Recommendation for monitoring for the development of CRS is included in SmPC section 4.2. Package leaflet sections 2 and 4 **Additional risk-minimization measures:** Patient Card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BO43309 See Section II.C of this summary for an overview of the post-authorization development plan.

CAR-T=chimeric antigen receptor (CAR) T-cell therapy; CRS=cytokine release syndrome; SmPC=summary of product characteristics.

Important Identified Risk: Tumor Flare	
Evidence for linking the risk to the medicine	Tumor flare has been observed in clinical data (Study NP30179) with *glofitamab*. It is a known risk with other immunomodulating agents, T-cell engaging therapies, checkpoint inhibitor therapies.
Risk factors and risk groups	Treatment with immunomodulatory agents is associated with tumor flare, and more frequent with hematologic malignancies than in patients with solid tumors.
Risk-minimization measures	**Routine risk-minimization measures:** SmPC section 4.4 and 4.8 Package leaflet section 2 and 4 **Additional risk-minimization measures:** HCP brochure
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BO43309 See Section II.C of this summary for an overview of the post-authorization development plan.

HCP= healthcare professional; SmPC=summary of product characteristics; TF=tumor flare.

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Serious infections have been observed in clinical data (Study NP30179) with *glofitamab*.
Risk factors and risk groups	Serious infections is a recognized risk associated with B-cell depletion treatment effect and a major cause of morbidity and mortality in patients with hematological malignancies. Underlying medical conditions in the patient population including history of recurring or chronic infections (e.g., chronic, active Epstein-Barr Virus) and prior immunosuppressive treatment are risk factors that may predispose to infections.
Risk-minimization measures	**Routine risk-minimization measures:** SmPC section 4.4 and 4.8 Recommendation for monitoring for the development of Serious Infections is included in SmPC section 4.4. Package leaflet section 2 and 4 **Additional risk-minimization measures:** No additional risk minimization measures

SmPC=summary of product characteristics.

Important Identified Risk: Immune effector cell-associated neurotoxicity syndrome (ICANS)	
Evidence for linking the risk to the medicine	IL-1 release from monocytes is likely to mediate ICANS along with CRS . GM-CSF-mediated stimulation of monocytes after CART cell treatment was linked to neuroinflammation in mice. In the clinic, myeloid cell-derived cytokines, most notably IL-1 and IL-6, have been shown to drive systemic inflammation which correlates with severe ICANS development. Additionally, patients experiencing severe ICANS often display elevated levels of the NMDA receptor agonist quinolinic acid, which is produced by stimulated macrophages. High concentrations of MCP-1, IP-10, IL-6, and IL-8 found during severe ICANS are indicative of activated macrophages and microglia. Collectively, these data indicate that myeloid cell hyperactivation contributes significantly to the development of ICANS. Considering that glofitamab can mediate the cytokine levels (including but not limited to: IL-2, IL-6, IL-8 and MCP-1), ICANS might occur after glofitamab exposure) **Non-clinical data:** Studies in cynomolgus monkeys showed that an increases in the release of granulocyte colony–stimulating factor (G-CSF), IFN-μ, IL-10, IL-17, IL-1 receptor antagonist (IL-1RA), IL-2, IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1 beta (MIP-1α and TNF-β were measured at 4 hours post dose, which, in general returned to baseline at 24 hours post dose A non-human primate study found that ICANS development was not CD19 antigen-specific, as CD20-targeted CART cells also led to ICANS in rhesus macaques. **Clinical trial data:** • Described or characterized by data from CD19-directed CAR-T therapies, symptoms of ICANS include tremor, dysgraphia, expressive aphasia, impaired attention, and apraxia • Phase I/II clinical trial data (Study NP30179)

Risk factors and risk groups	Older patients treated with glofitamab may have a higher risk of ICANS.
Risk-minimization measures	**Routine risk communication:** Section Dosage/Administration, Section Warnings and Precautions and Section Undesirable effects in the Swiss Product Information **Routine risk minimization activities recommending specific clinical measures to address the risk:** *Section Dosage/Administration of the Swiss Product Information* Columvi therapy should only be administered under the supervision of a healthcare professional experienced in the treatment of cancer patients and who has access to appropriate medical support to manage severe reactions associated with cytokine release syndrome (CRS). The treatment of neurological events or toxicity (including ICANS) are recommended as follows: Grade 1[1,2]: - Continue Columvi and monitor neurologic toxicity symptoms. - If ICANS, manage per current practice guidelines. Grade 2[1,2]: - 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 guideline. Grade 3[1,2]: - 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[1,2]:

	- 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 American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS. [3.] Consider the type of neurologic toxicity before deciding to withhold Columvi. [4.] See section 'Dosage/Administration' on restarting Columvi after dose delays. [5.] Evaluate benefit-risk before restarting Columvi. *Section Warnings and precautions of the Swiss Product Information* <u>*Neurological events*</u> Columvi may cause serious or life-threatening neurological toxicities, including immune effector cell-associated neurotoxicity syndrome (ICANS). Concomitant treatment with Columvi and other medicinal products that may cause dizziness or an altered state of consciousness can increase the risk of neurological toxicity. Patients should be monitored for signs and symptoms of neurotoxicity during treatment. The patient must be examined immediately at the first signs of neurotoxicity (including ICANS), a neurological evaluation should potentially be considered and, depending on severity, supportive care provided; Columvi should be temporarily or permanently discontinued depending on severity and the recommendations for treatment are to be adhered to (see "Dosage/Administration"). *Section Undesirable Effects of the Swiss Product Information* <u>*Neurotoxicity*</u> Among 145 patients who received COLUMVI, the most frequent neurologic toxicities of any grade were headache (10.3%), peripheral neuropathy (7.6%), dizziness or vertigo (6.9%), and mental status changes (4.8%, including confusional state, cognitive disorder, disorientation, somnolence, and delirium). Grade 3 or higher neurologic adverse reactions occurred in

	2.1% of patients and included somnolence, delirium, and myelitis. Cases of ICANS of any grade occurred in 4.8% of patients. **Other risk minimization measures beyond the Product Information:** ***Medicine's legal status*:** Columvi is a prescription-only medicine. **Additional risk-minimization measures:** <u>Patient Card*</u> The patient card informs patients of signs and symptoms of neurological toxicity so that medical attention can be sought appropriately. *Added to reflect local risk minimization measure in addition to EU RMP
Additional pharmacovigilance activities	None

Missing Information: Long-term safety	
Risk-minimization measures	**Routine risk-minimization measures:** No routine risk minimization measures **Additional risk-minimization measures**: No additional risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study NP30179 See Section II.C of this summary for an overview of the post-authorization development plan.

Missing Information: Safety in patients with prior CAR-T therapy	
Risk-minimization measures	**Routine risk-minimization measures:** No routine risk minimization measures **Additional risk-minimization measures**: No additional risk minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study NP30179 See Section II.C of this summary for an overview of the post-authorization development plan.

CAR-T = chimeric antigen receptor (CAR) T-cell therapy

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study NP30179:

Purpose of the study:

- To evaluate the safety, tolerability, and pharmacokinetics of glofitamab as single agent (and in combination with obinutuzumab) following obinutuzumab pre-treatment (Gpt) in patients with relapsed/refractory CD20 + B –cell Non-Hodgkin's Lymphoma

- The Marketing Authorization Holder shall provide a minimum of two years follow-up from the end of treatment of the last patient enrolled in the primary safety population of Study NP30179, including analyses of safety in patients with prior CAR-T therapy and safety by sex.

Study GO41944:

Purpose of the study:

- To evaluate the efficacy of glofitamab in combination with gemcitabine plus oxaliplatin compared with rituximab in combination with gemcitabine plus oxaliplatin on the basis of overall survival, progression-free survival, complete response rate, duration of objective response, duration of complete response, and time to deterioration in physical functioning and fatigue, and lymphoma symptoms
- To evaluate the safety and tolerability of glofitamab in combination with gemcitabine plus oxaliplatin compared with rituximab in combination with gemcitabine plus oxaliplatin on the basis of: incidence and severity of adverse events (severity determined according to NCI CTCAE v5.0), including cytokine release syndrome (CRS), with severity determined according to ASTCT CRS grading criteria; change from baseline in targeted vital signs; change from baseline in targeted clinical laboratory test results; tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events

II.C.2 Other Studies in Post-Authorization Development Plan

Study BO43309:

Purpose of the study:

- This non-interventional study will assess effectiveness of additional risk minimization measures (Healthcare Professional [HCP] Brochure, Patient Card). These measures will be implemented to intensify communication and medical and patient education around the important identified risks of CRS (Patient Card) and tumor flare (HCP Brochure).
- The main objective of the study is to evaluate the following process and behavioural indicators: receipt of the educational materials i.e., HCP Brochure and Patient Card, by the target population (glofitamab prescribers) and distribution of the Patient Card by prescribers to their patients; awareness, knowledge, comprehension, and self-reported adherence of prescribers with respect to tumor flare information included in the HCP brochure.