Regulatory Affairs

Kesimpta

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Ofatumumab
Product(s) concerned (brand name(s)):	Kesimpta
Document status:	Final
Version number of the RMP Public Summary:	3.1
Date of final sign off of the RMP Public Summary	02.05.2023

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 “Kesimpta” 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 “Kesimpta” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Kersimpta”

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This summary of the RMP for Kesimpta® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 Kesimpta's RMP.

I. The medicine and what it is used for

Kesimpta is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) (See SmPC for full indication). It contains ofatumumab as the active substance and it is given by subcutaneous injection at a dose of 20 mg/0.4mL.

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

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Kesimpta®, together with measures to minimize such risks and the proposed studies for learning more about Kesimpta®'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 authorised pack size — the amount of medicine in a pack is chosen so 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR 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 Kesimpta® is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Kesimpta® 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 Kesimpta®. 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 on 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);

Table 13-1 List of important risks and missing information

Important identified risks	None
Important potential risks	Serious infections, including opportunistic infections (e.g., PML, HBV reactivation) Malignancy Impaired immunization response, including vaccination of newborns after exposure in utero
Missing information	Safety in pregnancy and lactation Long-term safety of ofatumumab treatment Use in pediatric population Use in patients >55 years and Elderly population

II B: Summary of important risks

Table 13-2 Important potential risk Serious infections, including opportunistic infections (e.g., PML, HBV reactivation)

Evidence for linking the risk to the medicine	Considered 'important' as a change in the risk could have an impact on the benefit-risk of the product. There were no findings of opportunistic infections in adult monkeys of the non-clinical studies.
Risk factors and risk groups	The risk of infection may be higher in patients with decreased immunoglobulins, specifically IgG, and decreased leukocytes. Therefore, assessment of cases of serious infection, including OIs, will include evaluation of immunoglobulins and leukocytes, including lymphocyte and neutrophil counts. Patients with increased risk for OIs include immunocompromised patients, which includes those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies, those with severe active infections, including active acute or chronic hepatitis B infection, and elderly patients $\geq$ 65 years of age (patients > 55 were not included in the RMS trials). Since this is a potential risk, no attributable increase due to ofatumumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures:** SmPC Sections 4.3,4.4 and 4.8 PL Section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures:** None ALITHIOS study (COMB157G2399) Kesimpta long-term PASS (COMB157G2406) (Category 3 PASS).
Additional pharmacovigilance activities	

	See Part VI – II C of this summary for an overview of the post- authorization development plan.

Table 13-3 Important potential risk Malignancy

Evidence for linking the risk to the medicine	A weight of evidence approach (including review of the non-clinical and clinical findings noted with ofatumumab and a comprehensive literature review on the biology, mechanism of action and non-clinical and clinical findings of other anti-CD20 therapies) has not revealed data to suggest that treatment with ofatumumab would support or induce proliferation of transformed cells possibly leading to neoplasia.
Risk factors and risk groups	Immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies) are at increased risk for malignancies
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.3, PL section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures:** None
Additional pharmacovigilance activities	ALITHIOS study (COMB157G2399) Kesimpta long-term PASS (COMB157G2406) (Category 3 PASS). See Part VI – II C of this summary for an overview of the post- authorization development plan.

Table 13-4 Important potential risk Impaired Immunization response, including vaccination of newborns after exposure in utero

Evidence for linking the risk to the medicine	There were no cases impaired immunization response identified in MS clinical trial (Pool C2) with ofatumumab. Nonetheless, based on the mechanism of action, and the fact that this have been reported with other anti-CD20 therapies, there is a potential risk in patients on therapy with ofatumumab
Risk factors and risk groups	Since this is a potential risk, no attributable increase due to ofatumumab has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures**: SmPC Sections 4.4 and 4.5 PL Section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures**: None.
Additional pharmacovigilance activities	COMB157G2399 Sub Study: A sub-study to evaluate the effects of ofatumumab subcutaneous treatment on the immune responses following vaccination in patients with relapsing forms of multiple sclerosis (Category 3 PASS)

	See Part VI – II C of this summary for an overview of the post- authorization development plan.

Table 13-5 Missing information Safety in pregnancy and lactation

Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.6 and PL Section 2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Kesimpta PRIM study (OMB157G2407) (Category 3 PASS). See Part VI – II C of this summary for an overview of the post- authorization development plan

Table 13-6 Missing information Long-term safety of ofatumumab treatment

Risk minimization measures	**Routine risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures:** None ALITHIOS study (COMB157G2399)
Additional pharmacovigilance activities	Kesimpta long-term PASS (COMB157G2406) (Category 3 PASS). See Part VI – II C of this summary for an overview of the post- authorization development plan.

Table 13-7 Missing information Use in pediatric population

Risk minimization measures	**Routine risk minimization measures:** SmPC Sections 4.2 and 5.2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures**: None

Table 13-8 Missing information Use in patients >55 years and Elderly population

Risk minimization measures	**Routine risk minimization measures:** SmPC Sections 4.2 and 5.2 **Other routine risk minimization measures beyond the Product Information**: Legal status: Restricted medical prescription **Additional risk minimization measures**: None

Additional pharmacovigilance activities	ALITHIOS study (COMB157G2399) Kesimpta long-term PASS (COMB157G2406) (Category 3 PASS). See Part VI – II C of this summary for an overview of the post- authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Kesimpta®.

II.C.2. Other studies in post-authorization development plan

Table 13-9 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Kesimpta PRIM study (OMB157G2407) (Non-interventional study)	The primary objective is to estimate the proportion of major congenital malformations associated with exposure to ofatumumab during pregnancy among a) live births and b) live births, stillbirths and termination of pregnancy for fetal anomaly (TOPFA). The secondary objectives are to estimate the proportion of minor congenital malformation associated with exposure to ofatumumab during pregnancy and list the minor malformation by MedDRA preferred terms, to estimate the proportion of pregnancy outcomes associated with exposure to ofatumumab during pregnancy such as spontaneous abortions, stillbirths and elective terminations, the proportion of other adverse birth outcomes associated with exposure to ofatumumab during pregnancy including preterm birth, low birth weight and small for gestational age (SGA) and the frequency of adverse effects associated with exposure to ofatumumab during pregnancy and effects on immune system development in infants with follow-up of up to one year of age. The primary objective is to compare the event rates of malignancy and serious infections between ofatumumab-exposed patients with RMS and patients with RMS exposed to other approved disease modifying therapies (DMTs). The secondary objective is to estimate the event rates of malignancy and serious infections following ofatumumab treatment in patients with MS.
Kesimpta long-term PASS (COMB157G2406) (Non-interventional study).	The primary objective of the study is to evaluate the long-term safety and tolerability of ofatumumab 20 mg sc once every 4 weeks in subjects with RMS from the first dose of ofatumumab. The key secondary objective was to describe long-term efficacy of ofatumumab 20 mg sc once every 4 weeks in subjects with RMS from the first dose of ofatumumab.
ALITHIOS Study (COMB157G2399).	
COMB157G2399 Sub-Study	The primary objective of the sub-study was to characterize the humoral immune response to the tetanus-toxoid (TT) vaccine in subjects with RMS who are treated with ofatumumab 20 mg sc once every 4 weeks. The key secondary objective was to further characterize the humoral immune response to the TT vaccine, to the 13-valent pneumococcal conjugate vaccine (13-PCV), to 13-PCV boosted eight weeks later by 23-valent pneumococcal polysaccharide vaccine (23-PPV), to KLH neo-antigen and to the 2020-2021

Study short name	Rationale and study objectives
	seasonal quadrivalent influenza vaccine in subjects with RMS who are treated with ofatumumab 20 mg sc once every 4 weeks.