Swiss Summary of the Risk Management Plan (RMP) for Vedolizumab (ENTYVIO)

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Marketing Authorization Holder: Takeda Pharma AG

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 risk as well as to prevent or minimise them.

The RMP summary of ENTYVIO 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 ENTYVIO in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of ENTYVIO.

Summary of risk management plan for ENTYVIO (vedolizumab)

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

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

This summary of the RMP for Entyvio 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 Entyvio's RMP.

I. The medicine and what it is used for

Entyvio is authorised for ulcerative colitis and Crohn's disease (see SmPC for the full indication). It contains vedolizumab as the active substance and it is available as powder for concentrate for solution for infusion and as solution for injection, to be administered by intravenous infusion or subcutaneous injection respectively.

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

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002782/human_med_001751.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Entyvio, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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 Entyvio is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Entyvio are risks that need special risk management activities to further investigate or minimise 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 Entyvio. 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);

List of important risks and missing information	
Important identified risks	• Infusion-related reactions, including hypersensitivity reactions • Upper respiratory tract infections
Important potential risks	• Infections – Gastrointestinal infections and systemic infections (serious and nonserious) against which the gut constitutes a defensive barrier – Other serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML) • Malignancies • Liver injury
Missing information	• Use in Pregnancy and lactation • Long-term safety

II.B Summary of important risks and missing information

Important Identified Risk: Infusion-Related Reactions, Including Hypersensitivity Reactions	
Evidence for linking the risk to the medicine	Infusion-related reactions (IRRs), including hypersensitivity reactions (HSRs), are an important identified risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab clinical development program.
Risk factors and risk groups	Of the 61 patients in the Maintenance Phases of Studies C13006 and C13007 (N = 1434) who had AEs defined by the investigator as IRRs, 58 (95%) were HAHA-negative and 3 (5%) were HAHA-positive. There is the potential that patients who develop human antihuman antibodies (HAHA) to vedolizumab may have a predisposition to developing IRRs and HSRs; however, there is no clear correlation that seroconversion will predispose a patient to IRRs/HSRs.
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.8 SmPC section 4.2 where advice is given on monitoring during and after infusion SmPC section 4.4 where advice is given on monitoring for acute

	hypersensitivity and infusion-related reactions PL sections 2 and 4
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MLN-0002-401 See section II.C of this summary for an overview of the postauthorisation development plan.

Important Identified Risk: Upper Respiratory Tract Infections	
Evidence for linking the risk to the medicine	Upper respiratory tract infections are an important identified risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab clinical development program.
Risk factors and risk groups	There is no clear correlation between any identified risk factors and the onset of upper respiratory tract infections in the UC or CD population.
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.8 PL section 4
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MLN-0002-401 See section II.C of this summary for an overview of the postauthorisation development plan.

Important Potential Risk: Infections: Gastrointestinal Infections and Systemic infections (Serious and Nonserious) Against Which the Gut Constitutes a Defensive Barrier Other serious infections, including opportunistic infections such as PML	
Evidence for linking the risk to the medicine	Infections are an important potential risk based on the knowledge of the therapeutic class and the rates observed in the vedolizumab clinical development program. PML is known to be associated with natilizumab and was considered an AE of special interest in the vedolizumab clinical development program.
Risk factors and risk groups	Patients with prior exposure to immunosuppressants or immunomodulators (e.g., TNFα antagonists, natalizumab) may be at a greater risk of developing other serious infections, including opportunistic infections such as PML.
Risk minimization measures	**Routine risk minimisation measures:** SmPC section 4.8 SmPC section 4.4 where advice is giving on monitoring for infections and PML PL sections 2 and 4

	Additional pharmacovigilance activities: Patient Alert Card Healthcare Professional Guide
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MLN-0002-401 See section II.C of this summary for an overview of the postauthorisation development plan.

Important Potential Risk: Malignancies	
Evidence for linking the risk to the medicine	Malignancies are an important potential risk based on the knowledge of the therapeutic class. Overall, results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment, however long-term data is limited.
Risk factors and risk groups	Patients with prior exposure to immunosuppressants or immunomodulators (e.g., TNFα antagonists, natalizumab) may be at a greater risk for developing certain malignancies. Patients with IBD have an increased risk for colon cancer and NMSC.
Risk minimization measures	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MLN-0002-401 See section II.C of this summary for an overview of the postauthorisation development plan.

Important Potential Risk: Liver Injury	
Evidence for linking the risk to the medicine	The identification of liver injury as a new safety concern was a recommendation from the PRAC in 2016 (procedure number EMEA/H/C/PSUSA/00010186/201511) following a review of clinical and post-marketing events of liver injury. Vedolizumab does not require hepatic metabolism.
Risk factors and risk groups	Hepatobiliary manifestations may arise from chronic inflammation associated with IBD and severe IBD such as cholelithiasis, as well as the use of IBD medications. Patients with IBD receiving immunosuppressive therapy such as steroids, antimetabolites (such as 6-mercaptopurine, methotrexate, and azathioprine), or biologics are at risk of acquiring infections such as hepatitis B, which can cause liver injury. General risk factors for liver injury include excessive alcohol use, long-term or excessive use of certain medications (e.g., antimicrobials, anticonvulsants, and psychotropic drugs), blood-borne infections, and obesity (which can cause fatty liver).

Risk minimization measures	No risk minimisation measures

Missing Information: Use in Pregnancy and Lactation	
Risk minimization measures	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MLN-0002-401 See section II.C of this summary for an overview of the postauthorisation development plan.

Missing Information: Long-term Safety	
Risk minimization measures	No risk minimisation measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MLN-0002-401 See section II.C of this summary for an overview of the postauthorisation development plan.

II.C. Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Entyvio.

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

MLN-0002-401

Purpose of the study: To augment routine pharmacovigilance activities and aid in the further characterisation of the identified and potential risks, as well as the collection of data on populations that had no or limited exposure during the conduct of the phase 3 clinical program, as compared to other biologic treatments for IBD.