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Summary of the risk management plan (RMP) for Entyvio (vedolizumab)

This is a summary of the risk management plan (RMP) for Entyvio, which details the measures to be taken in order to ensure that Entyvio is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Entyvio, which can be found on Entyvio's EPAR page.

Overview of disease epidemiology

Ulcerative colitis and Crohn's disease are the two most common types of inflammatory bowel disease and are characterised by long-term inflammation of different parts of the gut. The conditions typically develop between the ages of 20 and 30 years, with an occasional onset in people over 50 years. In general, people with ulcerative colitis and Crohn's disease have been shown to have similar life expectancy as those without these diseases; however, there is a higher rate of death from colorectal cancer in patients with ulcerative colitis and Crohn's disease compared with the rest of the population.

The number of cases of ulcerative colitis and Crohn's disease are increasing worldwide. Up to about 500 in 100,000 people in Europe have ulcerative colitis, with up to about 24 new cases per 100,000 reported each year. For Crohn's disease, as many as 320 in 100,000 people in Europe are reported to have the condition, with up to about 13 new cases per 100,000 per year.

Summary of treatment benefits

In ulcerative colitis, Entyvio has been investigated in one main study in adult patients with moderate to severe active disease in whom conventional therapy or TNF-alpha antagonists were ineffective or could not be tolerated. Patients received either Entyvio or placebo (a dummy treatment) and the main measure of effectiveness was the proportion of patients whose symptoms improved after 6 weeks of treatment. Entyvio was shown to be more effective than placebo: 47% (106 out of 225) of patients who received Entyvio showed an improvement in symptoms, compared with 26% (38 out of 149) of patients who received placebo. In addition, the study also showed that Entyvio maintained the effect up to 52 weeks more effectively than placebo.

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Entyvio was also shown to be more effective than placebo at improving symptoms of Crohn's disease. In one main study in adult patients with moderate to severe active Crohn's disease in whom conventional therapy or TNF-alpha antagonists were ineffective or could not be tolerated, 15% (32 out of 220) of patients receiving Entyvio showed improved symptoms after 6 weeks of treatment, compared with 7% (10 out of 148) of patients on placebo. Similarly, in this study, the maintenance of the effect up to 52 weeks was more effective with Entyvio than with placebo.

Unknowns relating to treatment benefits

In the main and supporting studies of Entyvio for the treatment of ulcerative colitis and Crohn's disease, there was no apparent difference in how well the medicine worked based on a person's age, gender, race, or underlying medical conditions. The main clinical studies were one year long which provides information on relatively short term use of the medicine. However, there are some data on long-term effectiveness of Entyvio (beyond 1 year), and further longer term information is being collected in an ongoing clinical study.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Infusion-related reactions and hypersensitivity (allergic reactions)	In clinical studies, some patients (approximately 4%) who received Entyvio experienced mild to moderate infusion-related reactions, typically within 24 hours after treatment with Entyvio.	Entyvio should not be given to patients with a known allergy to Entyvio or any of its components. Doctors may give medicines to prevent allergic reactions before administering Entyvio. For the first two infusions, the doctor or nurse will monitor patients closely during the infusion and for approximately two hours after it is complete. For all subsequent infusions (after the first two), patients will be monitored during the infusion and for approximately 1 hour afterwards. Patients who have any signs of allergic reaction (such as wheezing, hives or itching) at any time during their treatment should contact their doctor immediately.

Upper respiratory tract infections. These include bronchitis (inflammation of the airways), influenza (flu), nasopharyngitis (inflammation of the nose and throat) and sinusitis (inflammation of the sinuses)	In clinical studies, approximately 25% of patients treated with Entyvio developed an upper respiratory tract infection at some point.	Upper respiratory tract infections are very common in the general population and not easily preventable.

Important potential risks

Risk	**What is known**
Gastrointestinal (gut) infections	Because Entyvio may affect the body's ability to fight infections in the gut, it may increase the chance of contracting an infection. It is important for patients to tell their doctor if they have fever or severe or prolonged symptoms of gut problems. Patients with any pre-existing infection should not start taking Entyvio unless their doctor advises them to do so.
Other serious infections	Natalizumab, a related medicine, has been shown to increase the risk of a rare but serious and sometimes fatal brain infection called progressive multifocal leukoencephalopathy (PML). While there were no reports of PML during clinical trials with Entyvio, there is not enough experience to date to completely rule out the possibility of an increased risk with Entyvio.
Off-label use (such as use in mild ulcerative colitis and Crohn's disease; use in children/adolescents; simultaneous use with biological immunosuppressant medicines)	This medicine has not been tested in either mild ulcerative colitis or mild Crohn's disease. This medicine has not been tested in individuals under 18 years of age. This medicine has not been tested in people also taking biological medicines (such as certain monoclonal antibodies) that suppress the immune system.
Cancer	The risk of developing certain cancers, such as colon cancer, is increased in patients with ulcerative colitis and Crohn's disease. Some medicines that help treat ulcerative colitis or Crohn's disease may increase the risk of some cancers. Overall, results from the clinical studies to date do not suggest an increased risk of cancer with Entyvio treatment; however, the number of cancers reported in the studies was small and long-term exposure to the medicine was limited. Long-term safety evaluations are ongoing.

Missing information

Risk	What is known
Use in pregnancy and breastfeeding	The effects of Entyvio in pregnant women are not known. Therefore, this medicine is not recommended for use during pregnancy unless the patient and doctor decide that the benefit clearly outweighs the potential risk to both woman and baby. Women who are pregnant, think they may be pregnant or are planning to have a baby should discuss this with their doctor before starting treatment with Entyvio. Women able to have children are advised to avoid becoming pregnant while using Entyvio. They should use adequate contraception during treatment and for at least 4.5 months after the last treatment. Women should tell their doctor if they are breastfeeding or planning to breastfeed. It is not known whether Entyvio passes into breast milk, and if so, what effect this may have on the baby.
Paediatric patients (under 18 years of age) and elderly patients (above 65 years)	Entyvio is not recommended for use in children or adolescents (under 18 years of age) due to the lack of information regarding the use of this medicine in this age group. In clinical studies of Entyvio, there were a total of 92 patients with Crohn's disease or ulcerative colitis who were 65 years of age or older, including 18 who were between 75 and 80 years of age. There was no difference in the safety of Entyvio or how well the medicine worked between these patients and younger patients.
Patients with liver/kidney /heart disease	The safety and effectiveness of Entyvio in patients with liver, kidney or heart disease have not been established.
Long-term safety	There is very limited safety information on patients who have taken Entyvio for longer than 4 years.
Patients who have had prior exposure to natalizumab, rituximab or concomitant use with other biological medicines (immunosuppressants)	Patients previously treated with natalizumab or rituximab have not been included in clinical trials for Entyvio. It is known that these medicines increase the risk of a rare but often fatal brain infection called progressive multifocal leukoencephalopathy, or PML. If patients who have received these medicines switch to Entyvio, they should be monitored for any signs and symptoms suggestive of PML (such as problems with balance, loss of sensation, memory loss). Should any symptom occur, then they should be referred to a neurologist for assessment. There are no studies in patients receiving biological immunosuppressant medicines at the same time as Entyvio.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Entyvio can be found on Entyvio's EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Entyvio's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Other serious infections, including opportunistic infections such as PML

Risk minimisation measure: Patient alert card and physician educational brochure
Objective and rationale: To inform healthcare professionals and patients of the potential risk of serious infections including opportunistic infections and PML, and to be aware of the neurological symptoms that may indicate an early onset of PML.
Description: Patient Alert Card: • To remind patients that they may be at risk of infections and should consult a healthcare professional if they are unwell. To alert patients to the early signs and symptoms of PML. • For patients to provide the Alert Card to healthcare professionals who may not be aware that the patient is being treated with Entyvio so that they are informed of the potential risks of serious infections and opportunistic infections, including PML. Physician Educational Brochure: A short pamphlet providing information to physicians: • To ensure that the identified and potential risks of treatment are made clear to the doctor, to aid discussion with the patient. • To ensure that doctors are aware of the need to monitor for neurological signs/symptoms of PML in view of the increased risk of PML associated with another monoclonal antibody (natalizumab) and to refer the patient to a neurologist as appropriate.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results

C130008 A Phase 3, Open-label Study to Determine the Long-Term Safety and Efficacy of Vedolizumab in Patients with Ulcerative Colitis and Crohn's Disease	An ongoing, uncontrolled open-label study to support the long-term safety and efficacy of Entyvio for the treatment of patients with moderate to severe ulcerative colitis or Crohn's disease	Long-term safety of Entyvio To determine the effect of long-term vedolizumab treatment on time to major inflammatory bowel disease-related events (hospitalisations, surgeries, and procedures) and health-related quality of life measurements	Ongoing	Final study report planned for 31 Mar 2017
MLN-0002_401 A Prospective, Observational, Cohort Safety Study of Vedolizumab Versus Other Biologic Agents for Inflammatory Bowel Disease	To increase routine pharmacovigilance activities and aid to further characterise 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 with other biological treatments for inflammatory bowel disease	To further characterise some of Entyvio's identified risks, potential risks and missing information.	Planned	01 Jul 2018 (interim) 30 Jun 2022 (final)

Studies which are a condition of the marketing authorisation

None of the above studies is a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 06-2014.