

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: May 7, 2014

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Drug Name(s): Entyvio (vedolizumab)

Therapeutic Class: Lymphocyte $\alpha 4\beta 7$ integrin receptor antagonist

Dosage and Route: Solution for infusion

Application Type/Number: BLA 125476, BLA 125507

Applicant/Sponsor: Takeda Pharmaceuticals

OSE RCM #: 2013-1641

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of BLA 125-476 and BLA 125-507 for vedolizumab to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). The application for vedolizumab was submitted to the Division of Gastrointestinal and Inborn Errors (DGIEP) by Takeda Pharmaceuticals on June 20, 2013 and administratively split into 2 BLAs, BLA 125-476 [Ulcerative colitis (UC)] and BLA 125-507 [Crohn's disease (CD)]. BLA 125-507 was initially granted priority review; however, the application received a major amendment during review of the BLA.

The Applicant submitted a proposed REMS for Entyvio to mitigate the potential risk of progressive multifocal leukoencephalopathy (PML). The Applicant's proposed REMS included a Medication Guide (MG) and a communication plan (CP) that comprised a

(b) (4) The Applicant submitted a timetable for submission of assessments at 18 months, 3 years, and 7 years.

1.1 PRODUCT BACKGROUND

Vedolizumab is an integrin transmembrane receptor antagonist¹ targeted to the human lymphocyte $\alpha 4\beta 7$ integrin. Specifically, Entyvio inhibits the migration of T lymphocytes into the gastrointestinal (GI) tract by inhibiting their adhesion to the ligand mucosal addressin cell adhesion molecule 1 (MADCAM 1).

Vedolizumab exhibits target mediated drug² disposition and the type of inflammatory bowel disease (IBD) (CD or UC) does not impact the pharmacokinetics of Entyvio. Vedolizumab specifically saturated $\alpha 4\beta 7$ integrin on memory helper T lymphocytes and did not decrease CD4 and CD8 trafficking into the Central Nervous System (CNS).

The Applicant proposed the following two indications:

1. Adult UC

- Reducing signs and symptoms, inducing and maintaining clinical response and remission, and mucosal healing, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNF α) antagonist.
- Dosing: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.

2. Adult CD

- Reducing signs and symptoms, inducing and maintaining clinical response and remission, and achieving corticosteroid-free remission in adult patients with

¹ Entyvio is hereinafter referred to as an integrin antagonist.

² For purposes of this review, the term "drug" means drug or biologic as defined under the FDCA and PHSA.

- moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF α antagonist.
- Dosing: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.

1.2 DISEASE BACKGROUND

The total population in the United States (US) with IBD is about 1.2 million patients. Specifically, the estimated UC and CD incidence rates in North America range from 0.6 to 19.2 new UC cases per 100,000 person-years and from 0 to 20.2 new CD per 100,000 person-years.³ Overall, more than one million patients in the US suffer from one of these two diseases.

UC is in part mediated by an influx of inflammatory cells into gut mucosal tissue. Patients with UC generally present with chronic relapsing disease, and periods of bloody mucoid diarrhea and abdominal pain may be followed by long quiescent periods between episodes. Patients may also exhibit systemic symptoms including fever, malaise, and weight loss, and severe colitis which can result in ischemic colitis requiring surgical colectomy. Colectomy is considered curative in UC, but it is associated with significant morbidity, including recurrent pouchitis in up to 25% of patients, fecal incontinence, and female infertility. Finally, patients with long-standing UC are at increased risk for colorectal cancer.

Current treatments used to treat UC include: mesalamine, corticosteroids, immunosuppressants, biologics (infliximab, adalimumab, golimumab), and surgery. The prevalent need for surgery, high relative risk of colon cancer, and substantial impact on quality of life (QOL) underscore the significant morbidity caused by this condition.

CD is in part mediated by an influx of inflammatory cells into gut mucosal tissue. In contrast to UC, the inflammation in CD may affect the entire GI tract and the entire thickness of the wall of the GI tract (transmural disease). Amongst other clinical manifestations, CD can cause abdominal pain, blood in the stool, ulcers, and severe diarrhea. Patients with severe CD may suffer from fatigue, skin disorders, inflammation of the liver, and other symptoms. Complications of CD include bowel obstructions, fistulas, and other health problems.

Current treatments used to treat CD include: mesalamine, corticosteroids, immunosuppressants, biologics (infliximab, adalimumab, certolizumab, and natalizumab), and surgery. There are currently 3 TNF α blockers used for CD: infliximab, adalimumab, and certolizumab. However, 20-40% of CD patients do not respond to induction therapy with TNF α blockers; further, 10 - 40% of patients who do respond to TNF α blockers lose response to them over time.⁴⁵ Further, patients exposed to TNF α

³ Mclean, et al. Vedolizumab for the treatment of ulcerative colitis and Crohn's Disease. *Immunotherapy*. 2012;4:883-898. doi:10.2217/imt.12.85.

⁴ Ole Haagen Nielsen, and Mark Andrew Ainsworth, Tumor Necrosis Factor Inhibitors for Inflammatory Bowel Disease. *N Engl J Med* 2013;369:754-62.

blockers are at increased risk of infections beyond the risk attributable to their underlying disease.⁶

Table 1 and Table 2 list the current drugs used to treat CD and associated boxed warnings derived from an independent, robust systematic review. Most of the drugs used to treat CD are also used to treat UC as discussed above and thus, in the interest of brevity and avoiding duplication, tables corresponding to the current treatments used for UC are not included but treatments were discussed above.

Despite multiple available therapies for the treatment of IBD, patients continue to experience symptoms or develop intolerance to or side effects from their treatment regimens. Importantly, vedolizumab is under consideration for the treatment of moderately to severely active CD and UC patients and is not under consideration for a milder disease indication.

⁵ Alexander Ford, Clinical Review: Ulcerative Colitis. *BMJ* 2013;346:f432 doi: 10.1136/bmj.f432 (Published 5 February 2013). *See also* Suneeta Krishareddy and Arun Swaminath, When combination therapy isn't working: Emerging therapies for the management of inflammatory bowel disease. *World J Gastroenterol* 2014 February 7; 20(5): 1139-1146.

⁶ Ole Haagen Nielsen, and Mark Andrew Ainsworth, Tumor Necrosis Factor Inhibitors for Inflammatory Bowel Disease. *N Engl J Med* 2013;369:754-62.

Table 1. Drugs used to treat CD⁷

Generic Name	U.S. Trade Name	Route	Half-Life	Mechanism of Action	FDA Approved for CD in Adults	FDA Approved for CD in Children
Adalimumab	Humira	Subcutaneous	10-18 days	TNF-alpha inhibitor	Yes	No
Certolizumab	Cimzia	Subcutaneous	~14 days	TNF-alpha inhibitor	Yes	No
Infliximab	Remicade	Intravenous	7.7-9.5 days	TNF-alpha inhibitor	Yes	Yes
Natalizumab	Tysabri	Intravenous	7-15 days	Prevents attachment of inflammatory immune cells to intestinal cell layers	Yes	No
Azathioprine	Azasan, Imuran	Oral, intravenous	5 hours	Purine synthesis inhibitor	No	No
6-Mercaptopurine	Purinethol	Oral	1-2 hours	Purine synthesis inhibitor	No	No
Methotrexate	Methotrexate	Intravenous, oral	3-15 hours	Dihydrofolate reductase inhibitor	No	No
Prednisone, prednisolone, 6-methyl- prednisolone, hydrocortisone, budesonide	Cortef, Entocort	Oral, topical, intravenous	8-54 hours	Binds glucocorticoid receptors in cytoplasm, where it upregulates anti-inflammatory genes	No*	No
Mesalamine	Asacol, Canasa, Pentasa, Lialda,	Oral, rectal	2-15 hours	Unknown	No	No
Sulfasalazine	Azulfidine	Oral	5-10 hours	Unknown	No	No

* Budesonide is approved by the Food and Drug Administration for mild to moderate Crohn's disease.

⁷ Table 1 and Table 2 derived from: AHRQ. Pharmacologic Therapies for the Management of Crohn's Disease: Comparative Effectiveness. Comparative Effectiveness Review Number 131, February 2014.

Table 2. Boxed warnings for drugs used to treat CD

Generic Name	Boxed Warning
Adalimumab	Malignancies (lymphoma and other malignancies, some fatal) Hepatosplenic T-cell lymphoma
Certolizumab	Serious infections (hospitalization, death, tuberculosis, bacterial sepsis, invasive fungal infections, opportunistic infections) Malignancies (lymphoma and other malignancies, some fatal)
Infliximab	Serious infections (hospitalization, death, tuberculosis, bacterial sepsis, invasive fungal infections, opportunistic infections) Malignancies (lymphoma and other malignancies, some fatal) Hepatosplenic T-cell lymphoma
Natalizumab	Progressive multifocal leukoencephalopathy (ETASU REMS Program)
Azathioprine	Malignancies
Methotrexate	Fetal death and/or congenital anomalies Reduced elimination in patients with impaired renal function, ascites, or pleural effusions Unexpectedly severe (sometimes fatal) bone marrow suppression, aplastic anemia, and gastrointestinal toxicity Hepatotoxicity, fibrosis, and cirrhosis Lung disease Diarrhea and ulcerative stomatitis Malignant lymphomas Tumor lysis syndrome Severe, occasionally fatal, skin reactions Potentially fatal opportunistic infections Soft tissue necrosis and osteonecrosis
6-mercaptopurine	No boxed warnings
Prednisone, prednisolone, 6-methyl-prednisolone, hydrocortisone, budesonide	No boxed warnings
Sulfasalazine	No boxed warnings
Mesalamine	No boxed warnings

1.3 REGULATORY HISTORY

June 7, 2000: IND 9125 submitted for MLN02

January 24, 2006: IND 9125 placed on clinical hold for insufficient information to allow the Agency to assess the risk of PML to subjects receiving MLN02.

April 4, 2006: Type A Meeting to discuss options for removing clinical hold. The Applicant proposed a risk minimization program for PML which included teaching site personnel and patients about the signs and symptoms of PML. Additionally, any new neurological signs or symptoms would be evaluated in few days for PML. Furthermore, a retrospective analysis for the JC virus would also be conducted for Phase 3 studies. The Agency indicated that every attempt should be made to follow patients for at least 2 years and requested the Applicant provide details regarding the specific signs and symptoms that would be used to identify cases of PML.

June 18, 2007: Applicant submitted a complete response to the clinical hold and included the Risk Assessment and Mitigation for PML (RAMP) algorithm. (see Section 3.2 for details)

July 19, 2007: Removal of clinical hold based on additional safety measures related to potential risk of PML.

After the removal of the clinical hold, additional meetings between the Agency and Applicant took place to continue discussions regarding the risk of PML and management within the clinical trials.

- December 11, 2007: Type C Meeting to continue discussions about PML risk management program, concomitant medications, neurologic exams, and JC virus testing
- September 26, 2008: Type C End of Phase 2 Teleconference to discuss outstanding clinical questions, and issues for Phase 3 activities. Discussions also included relationship between drug exposure and JC viremia and use of concomitant medications and prior therapies.
- July 13, 2010: Meeting to discuss Phase 3 development plan. Discussions also included use of concomitant medications and that a convincing demonstration that the risk of PML is lower than 1 in 1000 would require that at least 3000 patients be studied for at least 18 months with no cases of PML

July 20, 2011: A closed Gastrointestinal Drugs Advisory Committee (GIDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee meeting was held to discuss the potential risk of PML and risk management considerations for vedolizumab. The closed Joint Advisory Committee meeting was held to seek recommendations regarding Phase 3 study design features, including the number of patients and duration of study needed to exclude the risk of PML. The Advisory Committee did not come to consensus on an acceptable premarketing safety database size; however, the Advisory Committee strongly expressed that the duration of exposure is important and that 24 months could be considered as the minimum duration timeframe. The Applicant and the Agency agreed on a strategy which included a minimum of 900 patients to be exposed for 24 or more infusions with 4-months follow-up, as an acceptable premarket safety database to begin assessment of the risk-benefit of the product.

September 6, 2011: Type C follow-up Meeting to discuss the outcomes from the Joint GIDAC/DSaRM meeting. The Agency stated, assuming that there are no events, that the Applicant should study at least 1000 patients for a minimum of 24 months to rule out the risk of PML to an upper bound of 3/1000 patients. The Agency agreed that it was acceptable to discontinue JC virus measurements in the serum in the vedolizumab clinical trials.

July 24-25, 2012: Type C, post-Phase 3 meeting to discuss pivotal study data and clinical plan to support registration. The Agency stated that based on the information available, a REMS may be necessary to ensure that the benefits of vedolizumab outweigh the risks and encouraged the Applicant to submit a proposed REMS with its application.

November 6, 2012: Type C, Pre-BLA in which the Agency stated that due to new requirements under PDUFA V (i.e., the “Program”), the safety database at the time of original BLA submission, in contrast to proposed the 120 day safety update timeframe for submission, must include data on at least 900 patients that received 24 or more infusions. Additionally, the Agency agreed that the proposal to submit a proposed REMS for vedolizumab with the initial BLA was acceptable.

November 13, 2012: Fast track designation was granted for Entyvio in the treatment of UC and CD based on the unmet medical need for IBD.

June 24, 2013: BLAs for Entyvio were received. After initial review of the applications, DGIEP elected to split the application into two BLAs as based on the evidence submitted, the application related to the UC indication (BLA 125476) warranted priority review but the second application related to the CD indication (BLA 125507) warranted standard review.

The Applicant’s BLAs included a risk management plan and a proposed knowledge-focused MG and CP REMS to inform HCPs and patients about the theoretical risk of PML. Additionally, the Applicant proposed an observational study and enhanced pharmacovigilance to further characterize the potential and theoretical risks identified by the Applicant.

October 17, 2013: DRISK/DGIEP presented REMS options for vedolizumab to the REMS Oversight Committee (ROC). The ROC agreed that if vedolizumab is a safer drug than Tysabri, FDA should consider a less restrictive REMS. However, because the PML risk of vedolizumab is still uncertain, some members recommended a REMS for vedolizumab that is comparable to the Tysabri REMS until there is evidence that the drug does not have a similar PML risk. The ROC agreed that animal models demonstrating the vedolizumab is not active in the CNS would be persuasive that it does not have PML risk. Further, the ROC agreed that a voluntary program was unlikely to attract enough enrollees to provide information about the PML risk vedolizumab, and should be avoided.

December 9, 2013: The safety and efficacy of vedolizumab was discussed at a Joint GIDAC and DSaRM Advisory Committee Meeting. The Joint Advisory Committee recommended approval of vedolizumab for both proposed indications and recommended that postmarket risk assessment measures be employed to further quantify the potential risk of PML.

December 13, 2013: The Agency held a teleconference with the Applicant to discuss risk management, including REMS options. The Agency informed the Applicant of planned risk management strategies, including enhanced pharmacovigilance and the potential for a mandatory enrollment-based registry under a REMS or voluntary enrollment-based registry under a postmarketing requirement (PMR).

January 6, 2014: The Agency requested via email that the Applicant submit updated exposure tables stratified by months of exposure and number of infusions as of December 27, 2103 (i.e., a 6 month update to the 120 day safety update) for vedolizumab.

February 3, 2014: DRISK/DGIEP recommended that a REMS was not warranted for vedolizumab at the ROC meeting. The consensus amongst the ROC members was that while no cases of PML have been identified in clinical trials and FDA needs to communicate the potential risk of PML to prescribers to ensure that they will recognize and report cases of PML if they emerge. A CP REMS or non-REMS communication strategy could focus on communicating the potential risk to prescribers rather than restricting distribution.

March 13, 2014: FDA informed the Applicant that a REMS would not be required at this time. DGEIP encouraged the Applicant to disseminate the materials proposed under the REMS voluntarily.

March 21, 2014: Internal FDA meeting to discuss communication strategy regarding the potential risk of PML. The review team, Office of Communications, and Office of Health and Constituent Affairs (OHCA) recommended the following: (1) develop an internal question and answer (Q and A) document to address questions from external stakeholders after approval; (2) hold a stakeholder call within the first few weeks of product approval to inform key stakeholders about the potential risk of PML and other serious safety issues; (3) publish a FDA perspective piece in a journal (e.g, New England Journal of Medicine) describing the Agency's benefit-risk assessment of vedolizumab; and (4) encourage the Applicant to disseminate non-REMS communication materials to HCPs.

April 1, 2014: Internal meeting to finalize the postmarketing requirements and commitments for vedolizumab.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSIONS

- Takeda Pharmaceuticals, Proposed Risk Management Plan for vedolizumab, received June 24, 2013
- Takeda Pharmaceuticals, Proposed Entyvio REMS , received June 24, 2013

2.2 OTHER MATERIALS INFORMING THE REVIEW

- Takeda Pharmaceuticals, Clinical Overview for Vedolizumab, received June 24, 2013
- Takeda Pharmaceuticals, Clinical Safety Summary for Vedolizumab, received June 24, 2013

- Takeda Pharmaceuticals, proposed labeling for vedolizumab, received June 24, 2013
- Takeda Pharmaceuticals, Integrated Safety Summary (ISS) for Vedolizumab, received October 30, 2013
- Laurie Muldowney, Clinical Review, Vedolizumab, BLA 125476, November 20, 2013
- Laurie Muldowney, Clinical Review Addendum, Vedolizumab, BLA 125476, April 11, 2014
- Klaus Gottlieb, Clinical Review, Vedolizumab, BLA 125507, December 29, 2013
- Therese Cvetkovich, Review of Tysabri REMS Assessment Report, January 14, 2013
- FDA, Briefing Information for the December 9, 2013 Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee
- Laurie Muldowney, Medical Reviewer, DGIEP, Vedolizumab Clinical Trial Safety and Approach to Risk Assessment, Advisory Committee, December 9, 2013
- Kevin Bugin, Email to Applicant Requesting Updated Vedolizumab Exposure Data, January 6, 2014
- Kevin Bugin, Email to Applicant Requesting Clarifications to Postmarket Observational Study Protocol, January 17, 2014
- Takeda Pharmaceuticals, Response to Agency Questions, January 27, 2014
- Takeda Pharmaceuticals, Response to Agency Questions, January 31, 2014
- Kevin Bugin, Email to Applicant Requesting Submission of Pharmacovigilance Plan, including Enhanced Pharmacovigilance Plan, January 23, 2014
- Takeda Pharmaceuticals, Pharmacovigilance Plan and Response to Agency Questions, January 31, 2014
- Laurie Muldowney and George Neyarapally, Vedolizumab REMS Oversight Committee Presentation, February 3, 2014
- Takeda Pharmaceuticals, Draft Labeling and Medication Guide, March 11, 2014
- Kevin Bugin, Senior Regulatory Health Project Manager, DGIEP, Correspondence Regarding Postmarketing Requirements and Commitments, April 1, 2014
- Takeda Pharmaceuticals, Response to Agency Questions, April 3, 2014
- Kevin Bugin, Email to Applicant Recommending Implementation of Certain Elements of Communication Plan, April 10, 2014

3 RESULTS OF REVIEW OF PROPOSED ENTYVIO RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The development program for UC included a single, randomized, double-blind, placebo-controlled, phase 3 study (C13006) that evaluated vedolizumab. The primary objective in the Induction Phase was to determine the effect of vedolizumab induction treatment on clinical response in patients with moderately to severely active UC at 6 weeks. The primary objective in the Maintenance Phase of C13006 was to determine the effect of vedolizumab maintenance treatment on clinical remission in patients with moderately to severely active UC at 52 weeks.

For CD, the applicant submitted two randomized, double-blind, placebo-controlled studies (C13007 and C13011) that evaluated vedolizumab 300 mg as therapy for moderate to severe CD.

Induction was evaluated in C13007 and C13011; however, evaluation of maintenance was limited to C13007. The primary endpoint in C13007 and C13011 was clinical remission in patients with moderately to severe CD.

Efficacy: Summary

The key efficacy data are summarized briefly below. With respect to the proposed UC indication, the Applicant demonstrated that vedolizumab is efficacious in meeting its primary induction endpoint, clinical response at Week 6 in C13006. Regarding the proposed CD indication, Study C13007 met the primary endpoint to support the efficacy of vedolizumab for the induction of clinical remission in Crohn’s disease and the one maintenance trial met the primary endpoint.

Ulcerative Colitis:

Table 3: Clinical Response at Week 6 in Ulcerative Colitis (Study C13006)

Clinical Response	Placebo	Entyvio 300 mg
N	149	225
Number (%) achieving response	38 (25.5%)	106 (47.1%)
95% CI	(18.5, 32.5)	(40.6, 53.6)
Difference from placebo		21.7
95% CI for difference from placebo		(11.6, 31.7)
P value for difference from placebo		< 0.0001

Table 4: Clinical Remission at Week 52 in Ulcerative Colitis (Study C13006)

Clinical Remission	Placebo	Entyvio300 mg Q8W	Entyvio300 mg Q4W
N	126	122	125
Number (%) achieving response	20 (15.9%)	51 (41.8%)	56 (44.8%)
95% CI	(9.5, 22.3)	(33.1, 50.6)	(36.1, 53.5)
Difference from placebo		26.1	29.1
95% CI for difference from placebo		(14.9, 37.2)	(17.9, 40.4)
P value for difference from placebo		< 0.0001	< 0.0001

Vedolizumab was shown to be efficacious in the subgroup of patients who previously failed TNF α therapy, a patient population for whom surgical colectomy may be the only other treatment option.

Crohn’s Disease:

Table 5: Clinical Remission at Week 6 in Crohn’s Disease (Study C13007)

Clinical Remission	Placebo	Entyvio 300 mg
N	148	220
Number (%) achieving response	10 (6.8 %)	32 (14.5%)
95% CI	(2.7, 10.8)	(9.9, 19.2)
Difference from placebo		7.8%
95% CI for difference from placebo		(1.2, 14.3)
P value for difference from placebo		0.0206

Table 6: Clinical Remission at Week 52 in Crohn’s Disease (Study C13007)

Clinical Remission	Placebo	Entyvio300 mgQ8W	Entyvio300 mgQ4W
N	153	154	154
Number (%) achieving response	33 (21.6)	60 (39.0)	56 (36.4)
95% CI	(15.1, 28.1)	(31.3, 46.7)	(28.8, 44.0)
Difference from placebo		17.4	14.7
95% CI for difference from placebo		(7.3, 27.5)	(4.6, 24.7)
P value for difference from placebo		0.0007	0.0042

Study C13011 was conducted to investigate the efficacy of vedolizumab in patients who had previously failed TNF-alpha-blockers. The primary endpoint (achieving clinical remission) was not met.

3.2 SAFETY CONCERNS

The most frequently reported AEs in patients with UC (1279 patients in the safety database) and patients with CD (1850 patients in the safety database) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, and cough.

Results from the clinical program purportedly suggested no increased risk for malignancy (serious malignancy (excluding non-melanoma skin carcinomas) was diagnosed in 16 patients receiving vedolizumab (8 patients with UC and 8 patients with CD) during the phase 3 studies. with vedolizumab treatment); however, the number of malignancies was small and long-term exposure was limited.

In the UC patients, severe AEs, GI-related being the most common, occurred in 10% of patients in the placebo and vedolizumab groups. Four (4) deaths were reported in vedolizumab patients (1 patient within the controlled period and 3 patients within the uncontrolled period) but were considered unrelated to the drug. Amongst patients receiving vedolizumab for induction for Crohn’s Disease, serious AEs were reported by 7% of the placebo and vedolizumab groups. A

total of 9 deaths were reported in CD patients, with 5 deaths were reported during the study period of one of the two primary Phase III trials (4 in vedolizumab treated patients and 1 in a placebo treated patient). Two of these deaths were considered related to the study drug – one case of CD and sepsis and the other, septic shock.

The primary serious safety concerns associated with vedolizumab in both the UC and CD patients include:

- serious infections, including the potential risk of PML
- infusion-related reactions (IRR) and hypersensitivity; and
- hepatotoxicity.

Serious infections

Patients treated with vedolizumab are at increased risk for developing infections in light of the drug's antagonism of the lymphocyte receptor, $\alpha 4\beta 7$ integrin. The frequency of serious infections with vedolizumab treatment was 2% for patients with UC and 6% for patients with CD in phase 3 studies. The frequency of infections and infestations was higher in the vedolizumab group than in the non-ITT placebo group, but similar to the ITT placebo group. The most commonly reported infections in clinical trials occurring at a rate greater on vedolizumab than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Additional serious infections reported in patients treated with vedolizumab include anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, *Listeria* meningitis, giardiasis and cytomegaloviral colitis.

There is a potential risk for developing PML with vedolizumab because it is an identified risk for Tysabri (natalizumab), another integrin antagonist.^{8,9} PML is a demyelinating CNS disease that may rapidly progress to death and normally occurs in immunodeficient patient. PML pathogenesis is due to infection of the brain cells by the JC virus (JCV). The three characteristic symptoms of PML include visual deficits, motor impairment, and changes in mentation.¹⁰ There are no approved treatments for PML. In patients with PML, disease progression may slow or stop if the patient's immune system improves but patients with PML can rapidly progress to death. However, survivors often suffer from severe neurological sequelae such as serious problems with mentation and visual deficits (these sequelae are not usually reversible).

In contrast to vedolizumab, Tysabri is a monoclonal antibody directed against the $\alpha 4$ integrin subunit, and therefore, interacts with $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrin (see Figure 1). By preventing the $\alpha 4\beta 1$ integrin from binding to vascular cell adhesion molecule (VCAM)-1, natalizumab prevents

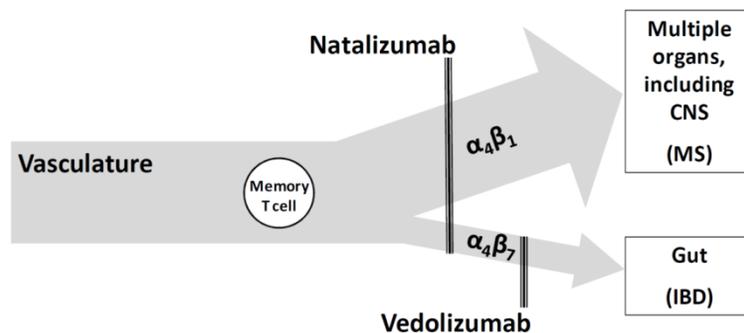
⁸ Roberta Diotti, et al. JC Polyomavirus (JCV) and Monoclonal Antibodies: Friends or Potential Foes? Clinical and Developmental Immunology 2013; <http://dx.doi.org/10.1155/2013/967581>.

⁹ Tysabri is approved for (1) the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations and (2) for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α .

¹⁰ Roberta Diotti, et al. JC Polyomavirus (JCV) and Monoclonal Antibodies: Friends or Potential Foes? Clinical and Developmental Immunology 2013; <http://dx.doi.org/10.1155/2013/967581>.

T lymphocytes from entering the brain and hence increases the risk of PML.¹¹ Risk factors associated with an increased risk of PML in patients taking Tysabri include: JC virus seropositivity, natalizumab exposure greater than 24 months, and a history of prior immunosuppressant therapy use. It is hypothesized that the difference in the specificity for the $\alpha_4\beta_1$ integrin binding between vedolizumab and natalizumab may provide protection from the risk of PML.¹²

Figure 1



The difference in mechanism of action and risk of PML is further supported by the non-clinical evidence. In particular, the Experimental Autoimmune Encephalomyelitis (EAE) model in Rhesus monkeys (a model developed for Multiple Sclerosis) showed that, in contrast to natalizumab, vedolizumab did not appear to inhibit CNS immune surveillance.¹³

The phase 3 vedolizumab studies employed a robust educational and surveillance program (Risk Assessment and Mitigation for PML (RAMP)) to mitigate the potential risk of PML by informing HCPs and patients and ensuring the rapid identification of PML in patients on vedolizumab. Specifically, the RAMP program entailed the following:

1. Education of health care professionals and patients participating in the clinical trials;
2. Systematic screening, using subjective and objective checklists, of patients at baseline and each scheduled study visit prior to infusion of study drug;
3. Prompt discontinuation of vedolizumab in cases involving new neurological symptoms potentially consistent with PML; and
4. Thorough and expedited evaluation of patients with new, unexplained neurological symptoms until PML is either excluded or confirmed.

Based on the Entyvio clinical trial data to date, no cases of PML have been identified out of 3326 patients exposed. Of these, 1056 patients were exposed to vedolizumab for at least 24 months. The Applicant's pre-approval safety database size was based on the Agency's recommendations that in order to provide an acceptable pre-approval assessment of PML risk in

¹¹ Kenneth L Tyler. PML therapy: "It's Déjà vu all over again." J. Neurovirol. 2013; DOI 10.1007/s13365-013-0191-9. To date, 359 natalizumab associated cases of PML have been reported out of over 115,000 treated patients (thus the risk is less than 0.1/1000 in JCV negative patients and about 11/1000 in JCV positive patients. See also Diotti, *supra* note 11. The risk of PML during natalizumab treatment is as high as 3.85/1000 patients.

¹² David Holmes. Integrin inhibitors go with the gut. Nature Reviews Drug Discovery 2013;12:411-412.

¹³ See Laurie Muldowney, Clinical Review, Vedolizumab, BLA 125476, November 20, 2013.

patients with UC and CD, a minimum of 900 patients should have received ≥ 24 vedolizumab infusions with 4 weeks post-infusion follow up. Based on the 1056 patients exposed to at least 24 months, a risk of PML between 0 and 2.8 cases/1,000 patients can be ruled out.¹⁴

IRR and hypersensitivity

In clinical trials with vedolizumab, hypersensitivity reactions have occurred including one case of anaphylaxis. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to vedolizumab may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

Hepatotoxicity

There were no imbalances in liver test abnormalities between randomized treatment groups in the Phase III controlled trials. Cases of liver injury, including serious liver injury, occurred during the vedolizumab clinical development program. Specifically, 4 patients reported serious adverse events of hepatitis during the controlled and open-label extension studies. All patients were treated with IV corticosteroids and recovered. Tysabri is also associated with liver injury and thus there is mechanistic plausibility with other biologics, including integrin antagonists.

3.3 REMS PROPOSED BY THE APPLICANT

The Applicant's BLAs included a risk management plan and a proposed knowledge-focused MG and CP REMS to inform HCPs and patients about the theoretical risk of PML. Additionally, the Applicant proposed an observational study and enhanced pharmacovigilance to further characterize the potential and theoretical risks identified by the Applicant. With respect to the observational study, the Applicant proposed that approximately 5000 patients (2500 patients per vedolizumab treatment cohort vs. other biologic agents) would be enrolled and followed for the course of the study. Based upon an expected discontinuation rate of 55% during the first 2 years and 10% thereafter, the Applicant anticipated that at least 1000 patients per cohort would be able to be followed for 24 months. Physicians would be encouraged to enter patients into this study, particularly those with prior natalizumab exposure. The (b) (4)

would all encourage HCPs to enroll their patients into the study. The Applicant proposed study assessments to be performed at least every 6 months by patients' treating physicians and emphasized that serious adverse events, adverse events of special interest (AESIs), and adverse reactions would be recorded at all visits. The Applicant stated that safety would be evaluated through: AESIs, which comprise the following:

- Serious infections (infections that are serious adverse events, including PML);
- Other clinically significant infections, not serious adverse events, that are classified as moderate or severe and require antibiotic treatment;

¹⁴ This calculation is based on the "rule of three." See Shail M. Govani, et al. Anti-Adhesion Therapies and the Rule of 3 for Rare Events. Am J Gastroenterol 2013; 108:1831 – 1832.

- Malignancies;
- Infusion-related reactions;

The sections below present the REMS proposed by the Applicant to mitigate the risks of PML.

3.3.1 REMS Goals



4 DISCUSSION

Both CD and UC cause a significant amount of morbidity and negatively impact patients' quality of life. In addition, CD patients have an increased risk of death as compared to UC patients. The benefits of treatment with vedolizumab as demonstrated in the pivotal studies included the following:

- Clinical response and remission in patients with moderate to severe UC and CD.
- The specific proposed indications are as follows:
 - Adult Ulcerative Colitis (UC): Inducing and maintaining clinical response and remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either corticosteroids, immunomodulators, or a tumor necrosis factor (TNF) blocker.
 - Adult Crohn's Disease (CD): Inducing and maintaining clinical response, achieving remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either corticosteroids, immunomodulators, or a tumor necrosis factor (TNF) blocker.

The serious risks of concern with vedolizumab are serious infections, including the potential risk of PML, IRR and hypersensitivity, and hepatotoxicity. To mitigate these risks, the Applicant has proposed labeling, enhanced pharmacovigilance, and an observational study. In addition, for the potential risk of PML, the Applicant has proposed a REMS that includes a MG and CP. The Applicant did not propose any training requirements or restricted distribution requirements for vedolizumab.

The GIDAC and DSaRM AC supported the approval of vedolizumab for both UC and CD based on the evidence of efficacy and safety. With respect to serious risks associated with Entyvio, the AC emphasized the importance of quantifying the potential risk of PML, conducting surveillance and further assessing PML, other serious infections, and hepatotoxicity, and ensuring that any risk mitigation strategies required beyond labeling to manage the potential risk of PML are not overly burdensome for prescribers.¹⁵

Serious infections

Vedolizumab, like other monoclonal antibodies, is associated with an increased risk of infections. The types of infections seen in clinical trials are consistent with the types of infections seen with other monoclonal antibodies. While there were no cases of PML reported in the clinical trials for vedolizumab, there is a potential risk for developing PML based on the known risk for Tysabri, which is another integrin antagonist. The mechanism of action for Entyvio is specific to binding at the $\alpha 4\beta 7$ integrin located in the GI tract; however, it is not possible to completely exclude an association between vedolizumab and PML. Based on the 1056 patients exposed to at least 24 months, a risk of PML between 0 and 2.8 cases/1,000 patients can be ruled out. Therefore, there is still *uncertainty* about the potential risk of PML in patients taking vedolizumab.¹⁶

¹⁵ The “benefits” and “risks” of the three main risk management options are discussed in detail in the backgrounder for the December 9, 2013 Advisory Committee (AC) meeting and were presented to the AC during the meeting. See FDA, Briefing Information for the December 9, 2013 Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee.

¹⁶ The Institute of Medicine has defined *uncertainty* as the lack or incompleteness of information and highlights that it depends on the quality, quantity, and relevance of data and on the reliability and relevance of models and assumptions (IOM, Ethical and Scientific Issues in Studying the Safety of Approved Drugs, 2012).

An important consideration in assessing the benefit-risk profile for Entyvio is other available alternatives. In contrast to CD, UC can be cured by colectomy. Thus, it is expected that prescribers would apply a more conservative benefit-risk calculus in UC compared to CD. However, based on feedback from IBD clinical trial experts, if vedolizumab had a comparable risk of PML as Tysabri, it is expected that Entyvio would be used very infrequently regardless of indication.

The acceptable risk of PML for approved drugs associated with PML varies depending on a several factors, including the condition being treated and patient risk factors. As a point of reference, the risk of PML in patients exposed to Tysabri is between <1/1000 (in JCV positive patients without prior immunosuppressant use and exposure to Tysabri between 1-24 months) and 11/1000 (in JCV positive patients with prior immunosuppressant use and exposure to Tysabri between 25-48 months).¹⁷ The overall (unstratified) PML incidence is estimated at of 2.6 per 1000 (95% CI 2.2 – 2.9), which is based on 285 confirmed Tysabri-associated PML cases world-wide through September 2012.¹⁸ The incidence of PML amongst subjects treated with Tysabri in clinical trials for MS and CD was approximately 1/1,000 (95% CI 0.2 to 2.8/1,000) with a mean exposure duration of 18 months. The incidence of the risk will depend on the disease being treated and risk factors, which are not known for Entyvio as no cases have been reported.

Below is a chart of drugs associated with PML and the risk management approaches employed for each respectively:

Table 7. PML risk associated with select, approved biologics and risk management approaches/regulatory actions¹⁹

Drug	Indication	Risk of PML	Risk management and REMS
natalizumab	MS, CD	0.1/1000 - 11/1000	Labeling (boxed warning) REMS: ETASU A, B, D, CP & MG
rituximab	NHL, CLL, RA, GPA, MPA	1/25000 (off-label SLE) and 0.4/100000 (RA)	Labeling (boxed warning) and MG as part of labeling REMS: No REMS
efalizumab	Withdrawn (PsA)	1/500 (>3 years use)	Labeling: Initially, boxed warning after case of PML emerged; then 3 fatal cases reported in Oct/Nov 2008; 2009 withdrawn REMS: No REMS

¹⁷ Tysabri (natalizumab) [package insert]. Cambridge, MA: Biogen Idec; 2013. (<http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=c5fdde91-1989-4dd2-9129-4f3323ea2962>. Accessed September 26, 2013)

¹⁸ KJ Baldwin and JP Hogg. Progressive multifocal leukoencephalopathy in patients with multiple sclerosis. *Curr Opin Neurol* 2013; 26:318-23.

¹⁹ Marilyn Pitts. Exploration of CDER's Risk Management Approaches to PML, an Adverse Event Common to Multiple Therapeutic Areas, March 5, 2013.

belatacept	Renal transplant rejection	2 cases	Labeling (Warnings and Precautions) REMS:REMS with a CP
mycophenolate	Organ transplant rejection	14/100,000 person-yrs	Labeling (Warnings) REMS: No REMS ^a

a: Note: There is an approved REMS for mycophenolate; however, the goal of the REMS is mitigate a risk of teratogenicity and not to mitigate a risk of PML.

Based on the currently available evidence, DGIEP and DRISK recommend not requiring a REMS to manage the serious risk of infections, including PML, for the following reasons:

- Vedolizumab binds specifically to the $\alpha 4\beta 7$ integrin located in the GI tract as compared with Tysabri, which binds to $\alpha 4\beta 7$ and $\alpha 4\beta 1$.
- The non-clinical evidence does not support an association between vedolizumab and PML.
- To date, zero cases of PML have emerged in the clinical trials program; therefore, the risk of PML is theoretical.
- The risk of PML has been measured up to 2.8 cases/1,000 patients, which is comparable to the overall risk of PML associated with Tysabri.

While the Applicant did propose a CP REMS, DRISK does not believe this is necessary at this time because a CP for a potential risk in which there is evidence suggestive that the risk is not associated with the product may create unnecessary confusion.²⁰ Therefore, DRISK believes the risk of serious infections, including PML, for vedolizumab can be adequately communicated through the prescribing information at this time. The prescribing information includes information in the Warnings and Precautions section of the label. Additionally, a MG will be maintained as part of labeling outside of a REMS.

²⁰ Further, when asked by an Advisory Committee member during the December 2013 Advisory Committee meeting, the Applicant failed to proffer evidence supporting their proposed REMS communication tools despite previous questions about this issue at the 2011 Advisory Committee meeting. Admittedly, there are inherent challenges in evaluating these tools in the premarket and postmarket setting (*see* T.A. Hammad, G. A. Neyarapally, S. Iyasu, et al. The future of population-based postmarket drug risk assessment: a regulator's perspective. Clin. Pharmacol. Ther. 2013;94:349–358) but the AC member emphasized that she did not have confidence in the Applicant's proposed REMS communication tools based in part on the lack of response to the questions about the effectiveness of proposed tools from the 2011 AC. Some CP tools, [REDACTED] (b) (4) proposed by the Applicant, employed in communication plans may not be not optimal [REDACTED] (b) (4)

[REDACTED] As mandated by the Prescription Drug Use Fee Act V (PDUFA V) commitments, FDA is currently developing new tools to enhance REMS communications to prescribers, patients, and other health care professionals (PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017).

Furthermore, the Applicant will be required to conduct a postmarketing observational study and enhanced pharmacovigilance to further characterize the risk of serious infections in patients receiving vedolizumab.

- A postmarketing observational study will be required to further characterize the potential risk of PML and assess the serious risks of infections. Specifically, the primary outcome of the study will be serious infections and secondary outcomes will include, but may not be limited to, progressive multifocal leukoencephalopathy (PML), malignancies, specific infections including gastrointestinal and upper respiratory infections, liver toxicity, serious adverse events (SAEs), other clinically significant infections that are not SAEs but are classified as moderate or severe and require antibiotic treatment, infusion-related reactions and adverse reactions.
- Enhanced pharmacovigilance will be required to ensure that quality data on any cases of serious infections, including PML, and cases of liver injury is obtained for postmarketing reports. In addition, expedited reporting will be required for reports of serious infections, liver injury, and tumors and malignancies, regardless of labeling status.

The review team also recommended external communication from the Agency regarding the risk of PML. The external communication strategy was believed to be necessary to ensure prescribers understood that while no cases of PML have been reported from clinical trials there is still uncertainty regarding the risk of PML associated with vedolizumab. Therefore, the external communication strategy will consist of the following:

- FDA will develop internal Qs and As to address potential questions from external stakeholders after approval. This will ensure consistent messaging to stakeholders regarding the Agency's action for vedolizumab and the determination that a REMS was not necessary. Additionally, the messages included in the Qs and As contain information regarding the postmarketing observational study to further characterize the risk profile of vedolizumab.
- FDA will hold an external stakeholder meeting shortly after drug approval to inform relevant stakeholders about the safety issues associated with vedolizumab with a focus on the potential risk of PML. The stakeholders include relevant patient and prescriber societies who are expected to utilize vedolizumab. These stakeholders, including relevant patient and prescriber societies, will then presumably utilize their own tools and approaches which are uniquely effective to communicate this safety-related information to their respective members.
- FDA will also publish a perspective piece in a journal (e.g., New England Journal of Medicine) describing the Agency's benefit-risk assessment of vedolizumab. The Agency believes this will provide stakeholders with transparency regarding the determination for why a REMS was not necessary at this time. Additionally, the perspective piece will describe the benefit-risk assessment and postmarketing strategies recommended for Entyvio (e.g., postmarketing observational study).

IRR and hypersensitivity

IRR and hypersensitivity reactions are known to occur with monoclonal antibodies administered by infusion. The clinical symptoms and outcomes associated with these reactions are consistent with the other monoclonal antibodies. These events can be adequately mitigated by the prescribing information and routine reporting requirements. The prescribing information will include information in the Warnings and Precautions and MG. Furthermore, the aforementioned postmarketing observational study and enhanced pharmacovigilance will be used to further characterize this risk in the postmarketing setting.

Liver injury

The cases of hepatotoxicity observed in the clinical trials were consistent with the types of cases that have been reported for Tysabri. Patients recovered with therapeutic treatment and discontinuation of vedolizumab. These events can be adequately mitigated by the prescribing information and routine reporting requirements. The prescribing information will include information in the Warnings and Precautions and MG. Furthermore, the aforementioned postmarketing observational study and enhanced pharmacovigilance will be used to further characterize this risk in the postmarketing setting.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for vedolizumab at this time. Vedolizumab has demonstrated efficacy in the treatment of UC and CD. The serious risks of concern with vedolizumab are serious infections, IRR and hypersensitivity, and hepatotoxicity. While the potential risk of PML cannot be completely ruled out, the available clinical and nonclinical data to-date, as well as the mechanism of action, suggest that vedolizumab is not associated with the risk of PML.²¹ The benefit-risk profile for vedolizumab is favorable and the risks can be mitigated through professional labeling, enhanced pharmacovigilance, continuation of the open label extension study, and postmarketing observational study. If a case of PML is reported in the postmarketing setting that is determined to be associated with the administration of vedolizumab, the benefit-risk profile and risk management strategy will need to be re-evaluated for vedolizumab.

Should the Division have any concerns or questions, or feel that a REMS may be warranted for this product, please contact DRISK.

²¹ Drug regulation entails a “regulatory paradox” – there is a “**tension between aversion to uncertainty and willingness to accept certain unknowns** about a drug **before approval** [emphasis added]” (I. Zineh and J. Woodcock. Clinical pharmacology and the catalysis of regulatory science: opportunities for the advancement of drug development and evaluation. Clin Pharmacol Ther. 2013;93(6):515-25.) Also, there can be substantial opportunity costs associated with an unwillingness to accept some level of uncertainty about a drug’s risks in the regulatory arena. This is especially important as no risk can be ruled out completely. See Eicher, et al. The risks of risk aversion in drug regulation, Nature Reviews Drug Discovery 2013;12:907-916. See also Gary E. Marchant & Rachel A. Lindor, Prudent Precaution In Clinical Trials Of Nanomedicines, 40 J.L. Med. & Ethics 831, 836 (2012) [discussing the regulation of innovative nanomedicines]: “...Here, where the argument for additional precaution is equivocal at best, any additional precautionary measures that are selected should be tempered and not unduly burdensome...”

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/s/

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