CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125499Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	March 3, 2014
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Subject:	Review evaluates if a REMS is needed for Plegridy
Drug Name:	Plegridy, Plegridy Pen (pegylated interferon beta-1a)
Therapeutic Class:	Interferon
Dosage form:	Sterile solution for injection
Application Type/Number:	BLA 125499
Applicant/sponsor:	Biogen Idec
OSE RCM #:	2013-1244

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the Biologics License Application (BLA) 125499 for Plegridy (pegylated interferon beta-1a[1]) to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). An application for Plegridy (pegylated interferon) was received by the Division of Neurology Products (DNP) from Biogen Idec Corporation on May 15, 2013. The Applicant did not propose a risk evaluation and mitigation strategy (REMS) for Plegridy.

1.1 BACKGROUND

Plegridy (pegylated interferon) is a novel type of interferon product with a proposed indication for the treatment adult patients with Multiple Sclerosis (MS). Pegylation is a process which involves the attachment of polyethylene glycol (PEG) to polypeptides to shield these peptides from enzymatic degradation and thereby increase the half-life of these products, along with potentially limiting adverse immunological effects. Although there are currently no approved pegylated interferon products for the treatment of MS, FDA has approved several different pegylated polypeptide products for a variety of indications in the past.

Plegridy is available as a single-use prefilled pen and a single-use prefilled syringe. A single prefilled pen or syringe contains 0.5 mL of solution of PLEGRIDY containing either 125 µg of pegylated interferon. A Plegridy Starter Pack is available containing two prefilled pens or syringes: 63 micrograms (dose 1) and 94 micrograms (dose 2). The proposed dosing regimen is 125 µg administered by subcutaneous injection once every 14 days. It is generally recommended that patients are titrated to ameliorate flu-like symptoms that can occur at treatment initiation with beta interferons. Patients should start treatment with 63 µg on day 1 (dose 1). On day 15 (14 days later) the dose is increased to 94 µg (dose 2), reaching the full dose of 125 µg by day 29 (after another 14 days) (dose 3).

MS is a chronic inflammatory disease which manifests in three forms: relapsing and remitting MS, primary progressive MS, and secondary progressive MS. In the early stages of MS, the majority of patients experience the relapsing and remitting form of the disease. Many of these patients progress to a secondary progressive disease after approximately six to ten years. MS causes significant morbidity, including chronic symptoms such as fatigue, spasticity, bladder and bowel problems, visual problems, depression, and other symptoms.

Patients with a history of relapsing and remitting MS are treated with disease-modifying anti-rheumatic drugs, which include the following:

Drug	Recommended dosage	Comments
Betaseron (interferon beta-1b)	0.25 mg SQ every other day	First interferon beta approved for relapsing-remitting MS
Avonex (pegylated interferon)	30 mcg IM weekly	Used as first line therapy for relapsing-remitting MS

[1] Pegylated interferon beta-1a is hereinafter referred to as pegylated interferon.

Drug	Recommended dosage	Comments
Rebif (pegylated interferon)	22 mcg or 44 mcg SQ 3 times a week	
Copaxone (glatiramer acetate)	20 mg SQ daily	Used as first line therapy for relapsing-remitting MS
Tecfidera (dimethyl fumarate)	120 mg twice daily for one week, then 240 mg twice daily	
Aubagio (teriflunomide)	7 or 14 mg tablet once daily	Boxed warning for risk of hepatotoxicity and teratogenicity
Gilenya (fingolimod)	0.5 mg once daily	Medication Guide and communication plan REMS to mitigate risk of bradyarrhythmia and atrioventricular block at treatment initiation, infections, macular edema, respiratory effects, hepatic effects, and fetal risk
Tysabri (natalizumab)	300 mg IV infusion over 1 hour every 4 weeks	Reserved for second line therapy; Approved as monotherapy only; available through a restrictive REMS due to risk of progressive multifocal leukoencephalopathy
Novantrone (mitoxantrone)	12 mg/m^2 IV infusion every 3 months	Reserved for rapidly advancing disease who have failed other therapies

SQ = subcutaneously; IM = intramuscular; IV = intravenously

Interferon beta is a disease modifying treatment which reduces the MS relapse rate by about 30% by inhibiting the expression of MHC class II on antigen presenting cells, inhibiting T cell activation and proliferation, and other mechanisms. Other agents which may be used first line include glatiramer acetate and fingolimod. Natalizumab and mitoxantrone are used second line based on their adverse effect profile.

1.2 REGULATORY HISTORY

A Pre-BLA meeting was held on March 12, 2013 and during this meeting FDA agreed that the Applicant's plan not to submit a REMS was reasonable but stated that the determination of the need for a REMS is a review issue.

On May 15, 2013, Biogen Idec Corporation submitted a BLA for Plegridy. The submission did not include a proposed REMS.

2 MATERIALS REVIEWED

The following is a list of internal materials that informed our review:

- Dr. Gerald Boehm. Clinical safety review for Plegridy (pegylated interferon), Division of Neurology Products, dated January 13, 2014

- Biogen Idec Corporation. Proposed Prescribing Information for Plegridy (pegylated interferon), received May 15, 2013
- Biogen Idec Corporation. Summary of Clinical Safety for Plegridy (pegylated interferon), received May 15, 2013
- Billy Dunn, Acting Deputy Director, Division of Neurology Products, Mid-Cycle Communication, November 5, 2013
- Sue Liu, Label, Labeling, Packaging, and Usability Study Review, October 17, 2013
- Nicole Bradley, Information Request, BLA 125499, Monday December 30, 2013

Below is a list of other materials that informed our review:

- Rehiana Ali, et al. Drugs in Development for Relapsing MS. Drug 2013;73:625-650.
- Nicholas R and Rashid W. Multiple sclerosis. Clin Evid Handbook. December 2012;464-466.
- Gary Owens, et al. Perspectives for Managed Care Organizations on the Burden of Multiple Sclerosis and the Cost-Benefits of Disease-Modifying Therapies. JMCP 2013;19:S41-S53.
- Bernd Kieseier and Peter Calabresi. PEGylation of interferon-B-1a: A Promising Strategy in Multiple Sclerosis. CNS Drugs 2012;62:205-214.
- Stephen Hauser, et al. Multiple Sclerosis: Prospects and Promise. Annals of Neurology 2013; 'Accepted Article', doi: 10.1002/ana.24009.
- AVONEX (pegylated interferon) injection for intramuscular injection, prescribing information, revised March 2013.
- J. Milton Harris and Robert B. Chess. Effect of Pegylation on Pharmaceuticals. Nature Reviews Drug Discovery 2003;2:214-221.
- Managing Multiple Sclerosis, Pharmacist's Letter, 2012.

3 REVIEW FINDINGS FOR PLEGRIDY

3.1 INTERFERON-BETA CLASS ADVERSE EVENT PROFILE

The most common adverse events associated with interferons are injection site reactions, which can include injection site necrosis and flu-like symptoms. Typically, injection site necrosis occurs within the first 4 months of therapy, although postmarketing reports have been received of injection site necrosis occurring over 1 year after initiation of therapy. Necrosis may occur at a single or multiple injection sites. Flu-like symptoms are often treated with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and glucocorticoids.

Serious adverse events associated with interferon-beta products include the following:

- Depression, suicide, and psychotic disorders have been reported in patients receiving interferon-beta products. Patients are advised to report any signs and symptoms and cessation of therapy is recommended.
- Hepatotoxicity: Hepatic injury, including elevated serum hepatic enzyme levels and hepatitis, some of which have been severe, has been reported. Asymptomatic elevation of hepatic transaminases (particularly ALT) is common.

- Congestive heart failure (CHF): While interferon beta does not have any known direct-acting cardiac toxicity, cases of CHF, cardiomyopathy, and cardiomyopathy with CHF have been reported.
- Anaphylaxis: Anaphylaxis has been reported as a rare complication of interferon beta use. Several allergic reactions, some severe, have occurred after prolonged use
- Decreased peripheral blood counts: Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia, have been reported.
- Autoimmune disorders: Autoimmune disorders of multiple target organs have been reported, including idiopathic thrombocytopenia, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis.

Approved labels for interferon-beta products include these serious risks of harm in the Warnings and Precautions section or Adverse Reactions section of the label.

3.2 OVERVIEW OF CLINICAL PROGRAM FOR PLEGRIDY

A two-year, double-blind, randomized, placebo-controlled Phase III clinical trial (Study 301, and its extension study, Study 302) conducted in the United States (US) formed the basis of the submission of the application for approval of Plegridy for the treatment of relapsing MS. (Together, these studies comprised 1512 patients, including 500 patients assigned to receive Plegridy every four weeks, 512 patients assigned to receive Plegridy every two weeks, and 500 patients assigned to receive placebo. Patients used a pre-filled pen (autoinjector) to administer the pegylated interferon.

3.2.1 Efficacy

The primary efficacy endpoint of the Phase 3 study was annualized MS relapse rate, the most common specified primary endpoint in MS product confirmatory trials, measured over the placebo-controlled year 1 of the study. Secondary endpoints included the proportion of patients relapsed and disability progression (based on change in the Expanded Disability Status Scale (EDSS) score) and MRI-related endpoints related to MS-induced lesions. During the second year of the study, patients originally randomized to placebo received pegylated interferon every two or four weeks, of the 1332 patients who received treatment in year 2, 608 (46%) the patients completed the treatment period and 625 (47%) were continuing treatment and assessments.

Patients on pegylated interferon experienced a statistically significant benefit relative to placebo on all primary and secondary endpoints. Regarding the primary endpoint, patients randomized to the every four week and every two week dosing regimens respectively experienced 27.5% and 35.6% reductions in MS relapse rates compared to patients in the placebo group.

3.2.2 Safety

Common adverse events

The safety profile of pegylated interferon was assessed in dose-ranging Phase 1 studies and in the pivotal Phase 3 study. A total of 1664 MS patients have been exposed to pegylated interferon. 1,350 MS patients were exposed to pegylated interferon for at least 6 months, 1,182 patients were exposed for at least 1 year, and 648 patients were exposed for at least 2 years.

The most common adverse drug reactions, occurring in more than 10% of patients included injection site erythema, influenza like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia. 6% (92/1,468) of MS subjects exposed to pegylated interferon experienced one or more AEs leading to discontinuation.

Flu-like symptoms were reported in 13% of placebo patients and 47% of patients in the two treatment groups. Most of these symptoms were mild or moderate and none were categorized as serious. The incidence of this adverse effect is consistent with other interferon products approved for the treatment of MS. Injection site reactions occurred more often in patients on pegylated interferon (11% placebo and 66% and 60% respectively in the every 2 week and every 4 week regimens) and again are a common adverse effect associated with interferon products approved to treat MS.

Serious adverse events

Of the MS subjects exposed to pegylated interferon, 20% (298/1,468) experienced one or more serious adverse events (SAEs). The only SAE that occurred in ≥1% of pegylated interferon exposed patients was MS relapse (13%, 185/1,468). Urinary tract infection (UTI) (n=9), and pneumonia (n=5) were the only other SAEs reported by at least five patients.

The mortality risk was higher in the placebo group than in the interferon treated patients. There did not appear to be a clustering of unusual cases of death.

Regarding other serious adverse events (SAEs), the proportion of patients experiencing a SAE was lower in the treatment groups than in the placebo group (7% and 9% versus 11%).

- Only two patients experienced serious injection site reactions – one patient experienced a serious event of injection site reaction and the other an injection site necrosis. Both of these events resolved with standard treatments.
- Consistent with other beta-interferons, the incidence of hepatic enzyme level elevation was higher in pegylated interferon patients (0% placebo, <1% pegylated interferon every 2 weeks, 0% pegylated interferon every 4 weeks). 2 pegylated interferon-treated subjects reported increases in ALT and AST ≥3 × ULN combined with increases in total bilirubin >2 × ULN. The approved beta interferon MS treatments are associated with a risk of severe hepatic injury and the labels for these products include information about this risk. Pegylated interferon patients had a higher risk of aminotransferase elevations 3x ULN compared to placebo. In addition, there were 2 “Hy’s Law” cases (aminotransferase elevations 3x ULN associated with total bilirubin >2xULN) potentially causally related to pegylated interferon. Based on comparisons to available data, the risks for aminotransferase elevations and hepatic injury with pegylated interferon appeared similar to other interferons. The available data are not sufficiently robust to rule out small but potentially important increases in risk for hepatic injury with pegylated interferon compared to other beta interferons. As with the approved beta interferons, the pegylated interferon label should include a Warnings and Precaution statement describing the liver injury risk.
- The incidence and severity of hematologic changes with pegylated interferon were consistent with approved interferon products.

- 3 patients experienced serious hypersensitivity reactions and all events resolved after discontinuation of pegylated interferon.

3.2.3 Product administration and safe use

During the device product review and Midcycle and late cycle meetings and respective communications with the Applicant, the Center for Devices and Radiological Health (CDRH) and the Division of Medicare Error Prevention and Analysis (DMEPA) raised a number of safe use issues related to the safe use of both the prefilled syringe and pen and potential medication errors. These issues relate to th (b) (4) and will be addressed before drug approval. These issues should be addressed by forthcoming human factors studies. Based on the usability studies that have been conducted, the aforementioned administration errors may result in underdosing or overdosing of Plegridy; however, they were not associated with serious safety issues in clinical trials. There is insufficient evidence to warrant a REMS for these issues at this time.

4 DISCUSSION

MS causes significant morbidity in the U.S. population, although it generally does not decrease life expectancy. Although beta interferons currently approved and used first line to treat MS are efficacious when compared to placebo, the sponsor and researchers emphasize the need for more convenient dosing regimens which may decrease injection-related events and other adverse effects such as anxiety which patients may experience when self-injecting, along with potentially addressing the problem of patient non-adherence with interferons, which is prevalent among MS patients.

In the clinical trials, pegylated interferon was found to be efficacious versus placebo with an acceptable safety profile. Pegylated interferon use was associated with a low incidence of serious safety issues and incidence of non-serious safety issues which are comparable to the incidence of safety issues associated with other interferon products approved for the treatment of MS based on studies of these other products outside of the Plegridy clinical development program. The proposed drug label for pegylated interferon is substantially similar to the drug label for pegylated interferon (Avonex) and includes the same risks in the Warnings and Precautions section of the label, including depression, hepatic injury, anaphylaxis, CHF, decreased peripheral blood counts, and autoimmune disorders.

Notably, none of the four interferon products currently indicated for MS have a required REMS program.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Plegridy (pegylated interferon). Plegridy has proven efficacy in the treatment of MS. The serious risks of concern associated with the administration of beta interferons are depression, hepatic injury, anaphylaxis, CHF, decreased peripheral blood counts, and autoimmune disorders and Plegridy's safety profile is consistent with the class of beta interferons. The only SAE that occurred in ≥1% of Plegridy exposed patients in the clinical trials was MS relapse and SAEs were reported slightly more frequently by placebo patients compared to Plegridy patients. Thus,

the benefit-risk profile for Plegridy is favorable and the risks can be mitigated though professional labeling.

Should DNP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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/s/

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03/03/2014

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