Peginterferon beta 1a (Plegridy)

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Peginterferon beta-1a is a newly approved disease modifying therapy (DMT) for the treatment of patients with relapsing forms of multiple sclerosis. Pegylation, the attachment of poly(ethylene glycol) (PEG) molecules to a protein prolongs the half-life and enables less frequent dosing.
Indication(s) Under Review in this document (may include off label)	Peginterferon beta 1a is indicated for the treatment of patients with relapsing forms of multiple sclerosis
Dosage Form(s) Under Review	**Pen** Injection: 125 micrograms of per 0.5 mL of solution in a single-dose prefilled pen Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled pen and 94 micrograms per 0.5 mL solution in a single-dose prefilled pen **Prefilled Syringe** Injection: 125 micrograms of per 0.5 mL of solution in a single-dose prefilled syringe Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled syringe and 94 micrograms per 0.5 mL of solution in a single-dose prefilled syringe
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Category C

Executive Summary

Efficacy	• The ADVANCE clinical study was a 2-year, double-blind, parallel group, Phase 3 study conducted with peginterferon beta-1a Q2W or Q4Wdosing to assess its safety and efficacy. • This study exhibited a significant benefit for the following outcomes versus placebo; the annualized relapse rate (ARR); proportion of patients relapsing; disability progression; Gd enhancing lesions; and, T2 lesions. • There are no head to head trials directly comparing peginterferon beta-1a to alternatives for the treatment of relapsing-remitting multiple sclerosis. Therefore,

	no claim can yet be made in the comparative efficacy of peginterferon beta-1a over other treatment modalities.
Safety	• The most common AEs associated with peginterferon beta-1a were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia (all had incidence more than 10% and at least 2% more than placebo). • The most commonly reported adverse event leading to discontinuation in patients treated with peginterferon beta-1a was influenza-like illness (in less than 1% of patients).
Potential Impact	• Peginterferon beta 1a has demonstrated a significantly lower annual relapse rate, disability progression and lesion burden on MRI in relation to placebo. • Peginterferon beta-1a is dosed every 14 days via subcutaneous injection. This decreases the number of monthly injections required by current therapies and removes the need to administer an intramuscular injection. This has the potential to decrease injection site reactions and allow better management of flu-like symptoms which develop with interferon injections.

Background

Purpose for review

Issues to be determined:

✔ Is there a need for therapeutic alternatives to be used as therapy in patients with relapsing, remitting Multiple Sclerosis?
✔ Does peginterferon beta-1a offer advantages to currently available therapies?
✔ Does peginterferon beta-1a offer advantages over current VANF agents?
✔ What safety issues need to be considered?
✔ Does peginterferon beta-1a have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations
Dimethyl fumarate	Oral agent, decreased lymphocyte count which needs to be monitored for, significant GI effects in some patients with impact tolerance and ability to stay on medication. Long term data on safety and efficacy is <10 yrs of treatment.
Glatiramer	Available in two dose regimens, QD or TIW
Interferon beta 1a (Avonex)	Once weekly IM injection, injection site reactions, flu like syndrome
Interferon beta 1a (Rebif)	Development of neutralizing antibodies, flu like syndrome with injections, injection site reactions
Interferon beta 1b (Betaseron, Extavia)	Development of neutralizing antibodies, flu like syndrome with injections, injection site reactions
Natalizumab	Monthly infusion, development of PML
Non-formulary Alternative (if applicable)	**Other Considerations**
Fingolimod	Oral agent, significant cardiac concerns, first dose monitoring is detailed and difficult for some facilities, Increased incidence of herpes infections.
Teriflunomide	Oral agent, potential side effect profile similar to leflunomide, extremely long half life that requires accelerated elimination procedure if serious adverse events develop. Has two Black Box Warnings.

Efficacy (FDA Approved Indications)

Literature Search Summary
MEDLINE and EMBASE were systematically searched using search terms peginterferon beta 1a, Plegridy, Multiple Sclerosis disease modifying therapy for randomized controlled trials published from 1980 through November 1, 2014. Additionally, articles relating to pharmacology, pharmacokinetics, tolerability and interactions were examined for inclusion. Published abstracts and websites of the Food and Drug Administration and European Medication Agency were reviewed for additional relevant information. The search was limited to studies performed in humans, in adults and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy
Currently available evidence (Please refer the reader to Appendix A for interpretation) is rated at a moderate level.

- The FDA approval was based on a single pivotal trial, ADVANCE was a multicenter, international, double-blind, parallel-group, phase 3 study involving 1516 patients randomly assigned 1:1:1 to pegIFN β-1a, 125 µg subcutaneously every 2 weeks or every 4 weeks or to placebo (with a dose escalation period for the initial 4 weeks). The primary endpoint was the determination of relapse rates after 1 year.
- Primary Outcome: Annualized relapse rate (ARR) over one year compared to placebo, the ARR at 1 year was significantly reduce following treatment with peginterferon beta-1a every 4 weeks and every 2 weeks at 27.5% (p=0.0114) reduction and 35.6% (p=0.0007) reduction respectively.
- Secondary Outcomes:
    - Number of new or newly enlarging T2 hyperintense lesions at 48 weeks; compared to placebo, the number of new or newly enlarging T2 hyperintense lesions at Year 1 was significantly reduced following treatment with peginterferon beta-1a every 4 weeks and every 2 weeks at 28% (p=0.0008) reduction and 67% (p<0.0001) reduction respectively.
    - Proportion of subjects relapsed at 48 weeks; compared to placebo, the risk of relapse over 1 year was significantly reduced by 26% (p=0.0200) following treatment with peginterferon beta-1a every 4 weeks and 39% (p=0.0003) following treatment with peginterferon beta-1a every 2 weeks.
    - Progression of disability as measured by EDSS Score at week 48; compared to placebo, the risk of progression of disability (12-week confirmation) over 1 year was reduced by 38% (p=0.0380) following treatment with peginterferon beta-1a (Plegridy®) every 4 weeks and 38% (p=0.0383) following treatment with peginterferon beta-1a (Plegridy®) every 2 weeks.
- The 2-year results from ADVANCE demonstrated the following (second year did not include a placebo arm)
    - Compared with Y1, annualized relapse rate (ARR) was further reduced in Y2 with every 2 week dosing (Y1: 0.230 [95% CI 0.183–0.291], Y2: 0.178 [0.136–0.233]) and maintained with every 4 week dosing (Y1: 0.286 [0.231–0.355], Y2: 0.291 [0.231–0.368]).
    - Patients starting peginterferon beta-1a from Y1 displayed improved efficacy versus patients initially assigned placebo, with reductions in ARR (every 2 weeks: 37%, p<0.0001; every 4 weeks: 17%, p=0.0906), risk of relapse (every 2 weeks: 39%, p<0.0001; every 4 weeks: 19%, p=0.0465), 12-week disability progression (every 2 weeks: 33%, p=0.0257; every 4 weeks: 25%, p=0.0960), and 24-week disability progression (every 2 weeks: 41%, p=0.0137; every 4 weeks: 9%, p=0.6243).
    - The ATTAIN study is currently on-going and is an extension of the ADVANCE study. The objectives of this 2-year global, dose-frequency-blinded, multicenter extension study are to determine the long-term safety.

Potential Off-Label Use

- Use in Secondary Progressive Multiple Sclerosis

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation
Warnings/Precautions	• Hepatic injury: monitor liver function tests • Depression and suicide • Seizures are associated with the use of interferon beta. Exercise caution when administering to patients with a seizure disorder • Anaphylaxis and other allergic reactions: serious allergic reactions have been reported as a rare complication of treatment with interferon beta. • Injection site reactions • Congestive heart failure: monitor patients with pre-existing significant cardiac disease for worsening of cardiac symptoms • Decreased peripheral blood counts

Safety Considerations

- Patients should be instructed in the use of measures to lessen influenza-like illness, pyrexia, headache, myalgia, chills
- Educate patients regarding development of depression or suicidal thoughts. Symptoms may include: new or worsening depression (feeling hopeless or bad about yourself), thoughts of hurting yourself or suicide, irritability (getting upset easily), nervousness, or new or worsening anxiety
- Development of injection site infection or necrosis.

Adverse Reactions	
Common adverse reactions	The most common adverse reactions (incidence ≥10% and at least 2% more frequent than placebo) were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia
Death/Serious adverse reactions	Warnings and precautions include hepatic injury, depression and suicide, seizure, anaphylaxis and other allergic reactions, injection site reactions, congestive heart failure, decreased peripheral blood counts and autoimmune disorders.
Discontinuations due to adverse reactions	Development of influenza type symptoms lead to treatment discontinuation in 2% of patients treated with pegylated interferon beta 1a given monthly and <1% of patients being treated every two weeks.

Drug Interactions

Drug-Drug Interactions

As a class, IFN was reported to be a weak inhibitor of CYP1A2 but no effects on the other major CYP enzymes or transporters. Therefore, peginterferon beta-1a was not considered to have a significant risk on impacting the pharmacokinetics of concomitantly administered medications.

Theophylline Derivatives: Interferons may decrease the metabolism of Theophylline Derivatives. Exceptions: Dyphylline.

Zidovudine: Interferons may enhance the adverse/toxic effect of Zidovudine. Interferons may decrease the metabolism of Zidovudine.

Risk Evaluation

As of February 15, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	• Plegridy® may be confused with Potiga™, Portia® • Pegylated interferon beta 1a may be confused with interferon alfa-2b, interferon alfacon-1, interferon beta, interferon gamma-1b, peginterferon alfa-2a, peginterferon alfa-2b • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Dosing and Administration

Patients should begin treatment of peginterferon beta-1a with 63 micrograms on day 1. On day 15 (14 days after initiation), the dose is increased to 94 micrograms. On day 29 (after another 14 days) the full dose of 125 micrograms is reached. Patients will continue with the full 125 microgram dose injected subcutaneously every 14 days thereafter (see Table 1). A peginterferon beta-1a Starter Pack containing two prefilled pens or syringes is available: 63 micrograms (dose 1) and 94 micrograms (dose 2).

Table 1: Schedule for Dose Titration

Dose	Time*	Amount (mcg)	Color of Pen or Syringe Label
Dose 1	On Day 1	63	Orange
Dose 2	On Day 15	94	Blue
Dose 3	On Day 29 and every 14 days thereafter	125 (full dose)	Grey

*Dosed every 14 days

Special Populations (Adults)

Dose adjustment is not required with body weight, gender, and age.

	Comments
Elderly	• No data identified
Pregnancy	• There are no adequate and well-controlled studies in pregnant women. • Peginterferon beta-1a has not been tested for developmental toxicity

	in pregnant animals. Monkeys given interferon beta subcutaneously every other day during early pregnancy had no teratogenic or other adverse effects on fetal development observed. Aboritfacient activity was evident after 3-5 doses.
Lactation	• It is not known whether this drug is excreted in human milk.
Renal Impairment	• Renal impairment can increase the Cmax and AUC for peginterferon beta 1a.. Results of a pharmacokinetic study in patients with mild, moderate, and severe renal impairment (creatinine clearance 50 to 80, 30 to 50, and less than 30 mL/minute, respectively) showed increases above normal for Cmax of 27%, 26%, and 42%, and for AUC, increases of 30%, 40%, and 53%. The half-life was 53, 49, and 82 hours in patients with mild, moderate, and severe renal impairment, respectively, compared to 54 hours in normal subjects. • End stage renal disease requiring hemodialysis two or three times weekly had AUC and Cmax of values that were similar to those of normal controls. Each hemodialysis session removed approximately 24% of circulating from the systemic circulation
Hepatic Impairment	• There are no dosage adjustments provided in the manufacturer's labeling
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- The VHA MS Center of Excellence Data Repository has a confirmed cohort of 26,238 Veterans with MS from 1999 - present. In 2013, there were 15,484 Veterans with a confirmed diagnosis of MS who made 132,903 unique outpatient visits. Since 2001, there has been a 73% increase in Veterans using VA specialty care and a 99% increase in specialty care visits. The numbers of Veterans with MS who are using VA services has increased steadily since the inception of the MSCoE. In FY2013 there were 8,200 patients receiving DMT agents to treat Multiple Sclerosis
- While pegylated interferon beta 1a has shown superiority to placebo with moderate clinical evidence, there is no data comparing it to other standard DMT agents. It could be considered in patients receiving a different form/route of interferon beta 1a to help combat issues such as injection site reactions, poor adherence or flu like syndrome.

References

1. Biogen Idec: Plegridy.2014. Available at http://www.biogenidec.com/therapies_plegridy.aspx?ID=20546. Accessed November 11, 2014.
2. Dossier for Plegridy. Provided by Biogen. 2014.
3. Calabresi PA, Kieseier BC, Arnold DL, Balcer LJ, Boyko A, Pelletier J, Liu S, Zhu Y, Seddighzadeh A, Hung S, Deykin A; ADVANCE Study Investigators. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. Lancet Neurol. 2014 Jul;13(7):657-65.
4. Hoy SM. Peginterferon Beta-1a: A Review of Its Use in Patients with Relapsing-Remitting Multiple Sclerosis. CNS Drugs. 2015 Feb 10.
5. Annibali V, Mechelli R, Romano S, Buscarinu MC, Fornasiero A, Umeton R, Ricigliano VA, Orzi F, Coccia EM, Salvetti M, Ristori G. IFN-β and multiple sclerosis: From etiology to therapy and back. Cytokine Growth Factor Rev. 2014 Oct 31.
6. Seddighzadeh A, Hung S, Selmaj K, Cui Y, Liu S, Sperling B, Calabresi PA. Single-use autoinjector for peginterferon-β1a treatment of relapsing-remitting multiple sclerosis: safety, tolerability and patient evaluation data from the Phase IIIb ATTAIN study. Expert Opin Drug Deliv. 2014 Nov;11(11):1713-20.
7. Reuss R. PEGylated interferon beta-1a in the treatment of multiple sclerosis - an update. Biologics. 2013;7:131-8.
8. Kieseier BC, Calabresi PA. PEGylation of interferon-β-1a: a promising strategy in multiple sclerosis. CNS Drugs. 2012 Mar 1;26(3):205-14
9. Hu X, Miller L, Richman S, Hitchman S, Glick G, Liu S, Zhu Y, Crossman M, Nestorov I, Gronke RS, Baker DP, Rogge M, Subramanyam M, Davar G. A novel PEGylated interferon beta-1a for multiple sclerosis: safety,

pharmacology, and biology. J Clin Pharmacol. 2012 Jun;52(6):798-808. Erratum in: J Clin Pharmacol. 2012 Sep;52(9):NP4-5.
10. Baker DP, Pepinsky RB, Brickelmaier M, Gronke RS, Hu X, Olivier K, Lerner M, Miller L, Crossman M, Nestorov I, ubramanyam M, Hitchman S, Glick G, Richman S, Liu S, Zhu Y, Panzara MA, Davar G. PEGylated interferon beta-1a: meeting an unmet medical need in the treatment of relapsing multiple sclerosis. J Interferon Cytokine Res. 2010 Oct;30(10):777-85.
11. Chase A. Multiple sclerosis: Pegylated IFN-β1a could lessen patients' injection burden. Nat Rev Neurol. 2014 Jun;10(6):308.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.