



Common Drug Review

Pharmacoeconomic Review Report

December 2015

Drug	Peginterferon beta-1a (Plegridy — subcutaneous injection)
Indication	Treatment of relapsing remitting multiple sclerosis to reduce the frequency of clinical exacerbations and to slow the progression of disability.
Listing Request	As per indication
Dosage Form(s)	63, 94 or 125 micrograms of peginterferon beta-1a in a pre-filled syringe or pre-filled pen for subcutaneous administration
NOC Date	August 10, 2015
Manufacturer	Biogen Canada Inc.

Note: At the time of the CADTH Common Drug Review submission for Plegridy, the price submitted by the manufacturer to CADTH was confidential. However, the manufacturer advised during the review that the submitted price does not need to remain confidential, as the submitted price is equivalent to the net wholesaler price at launch.

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ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
IFN	interferon
NMA	network meta-analysis
PegIFN	peginterferon beta-1a (Plegridy)
RRMS	relapsing-remitting multiple sclerosis

SUMMARY

Background

Peginterferon beta-1a (Plegridy) is a polyethylene glycol (Peg)–conjugated interferon beta-1a indicated for the treatment of relapsing forms of multiple sclerosis for adult patients to reduce the frequency of clinical exacerbations and to slow the progression of disability.¹ The manufacturer is requesting a listing in line with the Health Canada indication.

Peginterferon beta-1a is available in 63 mcg, 94 mcg, and 125 mcg pre-filled syringes or pens for subcutaneous injection at a confidentially submitted price of \$830.1538 per dose for all strengths. The recommended dosing of peginterferon beta-1a is 63 mcg at dose 1; 94 mcg at dose 2 in two weeks; and then 125 mcg every two weeks thereafter.

Summary of the Economic Analysis Submitted by the Manufacturer

The manufacturer submitted a cost analysis comparing the annual drug-acquisition cost of peginterferon beta-1a with that of the other interferons (IFNs) available for the treatment of relapsing-remitting multiple sclerosis (RRMS) (i.e., IFN beta-1a 30 mcg weekly, IFN beta-1a 22 mcg or 44 mcg three times weekly, and IFN beta-1b 250 mcg every other day), as well as glatiramer acetate (20 mg daily).² Comparator costs were from the April 2015 Ontario Drug Benefit Exceptional Access Program list prices. On the basis of a published network meta-analysis (NMA), clinical efficacy and safety was assumed to be similar between peginterferon beta-1a and its comparators.³ Health care resource use, other than drug usage, was also assumed to be similar among all comparators.

The annual cost of peginterferon beta-1a 125 mcg every two weeks is \$21,584 per patient, which is \$5,343 more than that of glatiramer acetate (\$16,241 per patient per year), \$1,509 to \$3,451 more than that of IFN beta-1b 250 mcg every other day (\$18,133 or \$20,075 per patient per year), \$1,484 more than that of IFN beta-1a 22 mcg three times weekly (\$20,100 per patient per year), cost-neutral to IFN beta-1a 30 mcg weekly (\$21,585 per patient per year), and \$2,885 less than IFN beta-1a 44 mcg three times weekly (\$24,469 per patient per year).

Key Limitations

Clinical Similarity to Comparators Uncertain

The assumption of clinical similarity of peginterferon beta-1a and other IFNs and glatiramer acetate is based on an NMA;³ no head-to-head trials of peginterferon beta-1a versus an active comparator are available. While methodologically well conducted, this manufacturer's NMA considered only annualized relapse rates and three-month and six-month confirmed disability progression in terms of efficacy outcomes. The inclusion of new and expanding lesion rates, as determined by magnetic resonance imaging, as well as the proportion of relapse-free patients at 12 months as outcomes, would have increased certainty in the efficacy of peginterferon beta-1a relative to other IFNs and glatiramer acetate. A recent Cochrane NMA⁴ did not find any significant difference in number of relapses or discontinuations due to adverse events (AEs) at 12 months between peginterferon beta-1a and IFN beta-1a 30 mcg weekly, IFN beta-1a 22 mcg or 44 mcg three times weekly, or IFN beta-1b 250 mcg every other day.⁴ For individual AEs, only the annualized rates of AEs that were reported by 5% or more of patients in the peginterferon beta-1a versus placebo ADVANCE trial⁵ were considered in the manufacturer's NMA.³ The comparative rates for peginterferon beta-1a versus comparators for other AEs, particularly those associated with glatiramer acetate, is unknown. Note that these NMA results should be interpreted with caution due to study heterogeneity in terms of patients' baseline

characteristics, study design, and study duration. For further detail, see the CADTH Common Drug Review (CDR) Clinical Report, Appendix 7.

Variation in Comparator List Prices

At the confidential submitted price of peginterferon beta-1a, the annual per-patient drug cost is equal to that of IFN beta-1a 30 mcg weekly at the price listed by the Ontario Drug Benefit Exceptional Access Program. Both Saskatchewan and Alberta reimburse IFN beta-1a 30 mcg at a lower list price per unit, leading to a lower annual cost than that of peginterferon beta-1a (\$21,038 and \$20,590 per patient, respectively). Although not a CDR-participating drug plan, the list price of IFN beta-1a 30 mcg is even lower in Quebec, leading to a lower annual cost (\$18,328 per patient). For price-reduction scenarios exploring these differences, see Appendix 1.

Secondary Comparators Omitted

While the other IFN treatments and glatiramer acetate are the most clinically appropriate comparators for peginterferon beta-1a (see CDR Clinical Report, section 1.2), other agents are available for the treatment of RRMS, and their relative price compared with peginterferon beta-1a may inform decision-making. The annual cost of peginterferon beta-1a is less than that of the biologics alemtuzumab (\$49,850 per patient in year 1, \$29,910 in year 2) and natalizumab (\$42,007 per patient per year), as well as less than the annual cost of the oral medications dimethyl fumarate (\$23,817 per patient in year 1, \$24,048 in subsequent years) and fingolimod (\$31,085 per patient per year). The annual cost of peginterferon beta-1a is \$1,885 more per patient than that of the oral agent teriflunomide (\$19,699 per patient per year). It should be noted that a recent Cochrane NMA⁴ found that peginterferon beta-1a, along with other IFNs, is less effective than alemtuzumab, natalizumab, and fingolimod in preventing clinical relapses over 12 months of therapy.

Issues for Consideration

Patient Convenience or Adherence

The biweekly dosing schedule of peginterferon beta-1a is less frequent than the dosing schedules of the other injectable IFNs that are indicated for the treatment of multiple sclerosis, which may increase patient convenience or adherence and increase the interval between some side effects, such as flu-like symptoms (see Patient Input Summary, CDR Clinical Report, Appendix 1). For the minority of patients who are unable to administer their own injections, the reduced dosing schedule of peginterferon beta-1a may decrease resources spent on administration by a nurse or support person.

Results and Conclusions

At the confidential submitted price of \$830.15 per dose, the annual cost of peginterferon beta-1a 125 mcg every two weeks (\$21,584 per patient per year) is identical to IFN beta-1a 30 mcg weekly, \$2,885 less expensive than IFN beta-1a 44 mcg three times weekly, but \$1,484 to \$3,451 more expensive than other available IFNs for the treatment of RRMS, and \$5,343 more than glatiramer acetate.

CDR conducted pricing scenarios considering the reduction in price required for peginterferon beta-1a to be cost-neutral to less expensive comparators, as well scenarios incorporating lower list prices available in some jurisdictions for IFN beta-1a 30 mcg weekly. Price reduction for peginterferon beta-1a varied between 4.6% and 16% when considering IFN options, and 24.6% versus glatiramer acetate.

Cost Comparison Table

Clinical experts have deemed the comparator treatments presented in Table 1 to be appropriate. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

TABLE 1: COST COMPARISON TABLE FOR THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

Drug/Comparator	Strength	Dosage Form	Price (\$)	Recommended Dose	Weekly Drug Cost (\$)	Annual Drug Cost (\$)
Peginterferon beta-1a (Plegridy)	63 mcg 94 mcg 125 mcg	SC syringe/pen	830.1538^a	Every two weeks: dose 1: 63 mcg; dose 2: 94 mcg; dose 3 and thereafter: 125 mcg	415	21,584
Other interferons						
Interferon beta-1a (Avonex)	30 mcg/0.5 mL (6 MIU)	Pre-filled syringe or pen	415.0900	30 mcg IM per week	415	21,585
Interferon beta-1b (Betaseron)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	110.0000	0.25 mg SC every other day	386	20,075
Interferon beta-1b (Extavia)	0.3 mg (9.6 MIU) powder for injection	Single-use vial	99.3593	0.25 mg SC every other day	348	18,133
Interferon beta-1a (Rebif)	22 mcg/0.5 mL (6 MIU) 44 mcg/0.5 mL (12 MIU)	Pre-filled syringe, cartridge, or pen	128.8433 156.8533	22 mcg to 44 mcg SC 3 times weekly	387 471	20,100 24,469
Biologics						
Alemtuzumab (Lemtrada)	12 mg/1.2 mL	IV solution	9,970.00 ^b	12 mg/day for five days followed by 12 mg/day for 3 days after 12 months	Weekly average: year 1: 959 year 2: 575	Year 1: 49,850 Year 2: 29,910
Natalizumab (Tysabri)	300 mg/15 mL	IV solution	3,231.2800	300 mg IV infusion every 4 weeks	808	42,007
Other injectable immunomodulatory						
Glatiramer (Copaxone)	20 mg/mL	Pre-filled syringe	44.4960	20 mg SC daily	311	16,241
Oral medications						
Dimethyl fumarate (Tecfidera)	120 mg 240 mg	Capsule	16.5164 33.0329	120 mg twice daily; after 7 days, increase to 240 mg twice daily	Week 1: 231; subsequent weeks: 462	Year 1: 23,817; subsequent years: 24,048
Fingolimod (Gilenya)	0.5 mg	Capsule	85.1650	0.5 mg daily	596	31,085
Teriflunomide (Aubagio)	14 mg	Tablet	53.9696	14 mg daily	378	19,699

IM = intramuscular; IV = intravenous; MIU = million international units; SC = subcutaneous.

Drug prices are taken from the Ontario Formulary Exceptional Access Program (September 2015) unless otherwise indicated, and do not include prescription fees, costs of dose preparation, or injection administration. Annual period assumes 52 weeks, or 13 × 4 weeks per year.

^a Manufacturer-submitted confidential price.

^b Régie de l'assurance maladie du Québec Liste des médicaments (September 2015).

APPENDIX 1: PRICE-REDUCTION ANALYSIS

As peginterferon beta-1a is more expensive than some comparators of interest, the CADTH Common Drug Review (CDR) conducted scenarios considering the percentage price reduction required for the cost of peginterferon beta-1a to be cost-neutral to the Ontario list prices of the most commonly prescribed interferon (IFN), the least expensive IFN beta-1a, the least expensive IFN, and glatiramer acetate (Table 2). Additionally, as variation in the list price of medications for relapsing-remitting multiple sclerosis (RRMS) exists across Canadian jurisdictions, CDR considered the price reductions required for the annual cost of peginterferon beta-1a to be cost-neutral to the lowest price for IFN beta-1a 30 mcg among CDR-participating jurisdictions, as well as to the lowest list price of a Canadian jurisdiction (Table 2).

TABLE 2: CDR SCENARIOS EXPLORING PRICE REDUCTIONS REQUIRED FOR PEGINTERFERON TO BE COST-NEUTRAL TO VARIOUS COMPARATORS

Scenario	Confidential Annual Cost of PegIFN	Annual Cost of Comparator	Price Reduction Required
Price reduction needed to equal most-prescribed IFN ^a (IFN beta-1a 30 mcg weekly, Avonex, ODB)	\$21,584	21,585	None
Price reduction needed to equal lowest CDR-participating jurisdiction list price ^b for IFN beta-1a 30 mcg weekly (Avonex, Alberta Health)		20,590 ^b	4.6%
Price reduction needed to equal lowest Canadian jurisdiction list price ^c for IFN beta-1a 30 mcg weekly (Avonex, RAMQ)		18,328 ^c	15.1%
Price reduction needed to equal least expensive IFN beta-1a (IFN beta-1a 22 mcg three times weekly, Rebif 22)		20,155	6.6%
Price reduction needed to equal least expensive IFN (IFN beta-1b 250 mcg every other day, Extavia)		18,133	16.0%
Price reduction needed to equal least expensive IFN (IFN beta-1a 30 mcg weekly, Avonex)		16,278	24.6%
Price reduction needed to equal glatiramer acetate (20 mg daily)			

CDR = CADTH Common Drug Review; EAP = Exceptional Access Program; IFN = interferon; ODB = Ontario Drug Benefit; PegIFN = peginterferon beta-1a; RAMQ = Régie de l'assurance maladie du Québec.

Note: Annual costs are calculated using ODB EAP list prices (September 2015) unless otherwise indicated.

^a "Most-prescribed IFN" is based on nationwide public-plan data from IMS Pharmastat, considering market share by number of claims from January 2014 through June 2015. Rebif 44 mcg is the most frequently reimbursed IFN in some individual jurisdictions (Alberta, British Columbia), and is more expensive than PegIFN (using the ODB EAP pricing as well as the list prices of Alberta and British Columbia).

^b Based on the Alberta Health Drug Benefit list price for Avonex of \$395.9696 per dose (September 2015).

^c Based on the RAMQ liste de médicaments price for Avonex of \$352.4625 per dose (September 2015).

While the annual per-patient cost of peginterferon beta-1a is cost-neutral to that of IFN beta-1a 30 mcg weekly using the Ontario Drug Benefit list price, it would need to be reduced by 4.6% to be cost-neutral in the CDR-participating jurisdiction with the least expensive list price, and by 15.1% in the Canadian jurisdiction with the least expensive list price for IFN beta-1a 30 mcg weekly. Similarly, the annual cost of peginterferon beta-1a would need to be reduced by 6.6%, 16.0%, and 24.6% to be equal to the Ontario Drug Benefit list price, based on annual per-patient costs of the least expensive IFN beta-1a, the least expensive IFN, and glatiramer acetate, respectively.

APPENDIX 2: REVIEWER WORKSHEETS

TABLE 3: SUMMARY OF MANUFACTURER'S SUBMISSION

Drug Product	Peginterferon beta-1a (Plegridy)
Treatment	63 mcg at dose 1, 94 mcg at dose 2 after two weeks, then continuing with 125 mcg every two weeks thereafter.
Comparators	Interferon beta-1a (Avonex) 30 mcg per week Interferon beta-1b (Betaseron) 250 mcg every other day Interferon beta-1b (Extavia) 250 mcg every other day Interferon beta-1a (Rebif) 22 mcg or 44 mcg three times weekly Glatiramer acetate (Copaxone) 20 mg daily
Study Question	Not specified but represents: What is the relative annual acquisition cost of Plegridy (PegIFN) compared with other available interferons and glatiramer acetate for the treatment of RRMS?
Type of Economic Evaluation	Cost analysis
Target Population	Not specified, assumed general RRMS population
Perspective	Not specified, assumed public drug payer
Outcome Considered	Annual drug-acquisition cost
Key Data Sources	
Cost	Manufacturer's confidential submitted price for PegIFN, ODB Exceptional Access Program Formulary (April 2015) for comparators
Clinical Efficacy	Published NMA ³
Harms	Non-statistical comparison within NMA publication ³
Time Horizon	One year
Results for Base Case	Annual acquisition cost of IFN 125 mcg Q2W (Plegridy): \$21,584; Comparator annuals costs ranged from \$16,241 per patient per year to \$24,469 (Table 4).

IFN = interferon; NMA = network meta-analysis; ODB = Ontario Drug Benefit; PegIFN = peginterferon beta-1a; Q2W = every two weeks; RRMS = relapsing-remitting multiple sclerosis.

Manufacturer's Results

The manufacturer submitted a cost analysis that included only drug-acquisition costs over a one-year time horizon comparing peginterferon beta-1a with other interferons available for the treatment of relapsing-remitting multiple sclerosis (RRMS) as well as to glatiramer acetate.

The manufacturer's calculated drug costs for its chosen comparators were identical to those calculated by the CADTH Common Drug Review (CDR) in Table 1; therefore, only the manufacturer's summary and relative costs are presented in Table 4.

Glatiramer acetate was \$5,343 less per patient per year than peginterferon beta-1a. The annual costs of the other interferons available for the treatment of RRMS ranged from \$3,451 less than that of peginterferon beta-1a to \$2,885 more. The annual drug cost derived from the confidentially submitted price of peginterferon beta-1a 125 mcg every two weeks is cost-neutral to the annual drug cost of interferon (IFN) beta-1a 30 mcg every week.

TABLE 4: MANUFACTURER’S SUMMARY OF RELATIVE ANNUAL COSTS OF COMPARATORS

Comparator	Dosing	Annual Drug-Acquisition Cost (\$)	Cost Relative to PegIFN (\$)
Glatiramer acetate (Copaxone)	20 mg daily	16,241	-5,343
IFN beta-1b (Extavia)	250 mcg every other day	18,133	-3,451
IFN beta-1b (Betaseron)	250 mcg every other day	20,075	-1,509
IFN beta-1a (Rebif)	22 mcg three times weekly	20,100	-1,484
PegIFN beta-1a (Plegridy)	125 mcg every 2 weeks	21,584	Reference
IFN beta-1a (Avonex)	30 mcg every week	21,585	1 ^a
IFN beta-1a (Rebif)	44 mcg three times weekly	24,469	2,885

IFN = interferon; PegIFN = peginterferon beta-1a.

Adapted from Tables 2 and 3 in manufacturer’s pharmacoeconomic submission.²

^a Reported as \$0 in manufacturer’s submission; actual annual difference is \$0.68, i.e., effectively cost-neutral.

CADTH Common Drug Review Results

CDR reviewers were able to replicate the manufacturer’s calculations regarding the total and relative drug-acquisition costs of peginterferon beta-1a and its comparators.

After consultation with a clinical expert, CDR reviewers retrieved utilization data for IFN and glatiramer acetate from IMS Pharmastat from January 2014 through June 2015 (Table 5). When all public drug plans reporting IFN reimbursement were included, IFN beta-1a (Avonex 30 mcg) was the most commonly prescribed IFN (39% of claims), followed by IFN beta-1a (Rebif 44 mcg), and IFN beta-1b (Betaseron). These market shares remained stable between quarters throughout the retrieved 18-month period, although there were variations across the reporting jurisdictions. These market shares were used for price-reduction scenario analyses as described in detail in Appendix 1.

TABLE 5: CANADA-WIDE PUBLIC INTERFERON MARKET SHARE BY NUMBER OF CLAIMS (JANUARY 2014 THROUGH JUNE 2015)

Trade Name	Strength	Total Claims	Market Share, IFN Only	Market Share, Including Glatiramer Acetate
IFN beta-1a (Avonex)	30 mcg	5,872	39.1%	12.1%
IFN beta-1b (Betaseron)	0.3 mg	2,960	19.7%	6.1%
IFN beta-1b (Extavia)	0.3 mg	311	2.1%	0.6%
IFN beta-1a (Rebif)	22 mcg	1,071	7.1%	2.2%
IFN beta-1a (Rebif)	44 mcg	4,797	32.0%	9.9%
Glatiramer acetate (Copaxone)	20 mg	33,566	Excluded	69.1%

IFN = interferon.

Data retrieved from IMS Pharmastat January 2014 through June 2015, restricted to public payers.

As the annual cost of peginterferon beta-1a is cost-neutral to the most commonly prescribed IFN (beta-1a 30 mcg weekly) and less expensive than the next most commonly prescribed IFN (beta-1a 44 mcg three times weekly), peginterferon beta-1a is likely to increase costs to drug plans only if its use replaces that of less expensive IFNs (Appendix 1). However, if patients who would have received glatiramer acetate or the oral medication teriflunomide (\$19,699 per patient per year; 5,531 claims from January 2014 to June 2015) are instead prescribed peginterferon beta-1a, per-patient costs to drug plans would increase.

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