Interferon Beta 1b (Extavia®)

Abbreviated National Drug Monograph
September 2010
VA Pharmacy Benefits Management Services,
Medical Advisory Panel and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. The manufacturer's labeling should be consulted for detailed information when prescribing interferon beta-1b VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.

Executive Summary

- Biologic drugs do not have generic equivalents
- There are no head to head trials of Extavia® vs. Betaseron® available.
- The FDA did not grant Extavia® therapeutic interchangeability with Betaseron®, but approved Extavia® with the same active ingredient and registration trials as Betaseron® 250 mcg.
- Novartis signed an agreement with Bayer Schering Pharma AG that gives Novartis the rights to its own branded version of interferon beta-1b
- The differences between the two IFN beta-1b products are that the Extavia® brand comes with a 27-gauge needle, packaged with 15 vials for a 30 day supply, while the Betaseron® brand has 30-gauge needles, packaged with 14 vials for a 28 day supply. The difference in package size correlates to 12 packages for Extavia® for a year of therapy versus 13 for Betaseron®.

Introduction

Interferon beta-1b (IFN beta-1b) is an immunomodulator used in the treatment of Multiple sclerosis (MS). It is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques. On August 14, 2009 the FDA approved Extavia®, a new branded version of interferon beta-1b, is the same product as Betaseron®. Extavia® 250 mcg contains the same active ingredient as Betaseron® 250 mcg, with a separate Biologic License Agreement (BLA) filed by Novartis.

Background

- Novartis signed an agreement with Bayer Schering Pharma AG that gives Novartis the rights to its own branded version of interferon beta-1b. (Media release, personal correspondence)
  - 1993: Chiron began manufacturing Betaseron® for Berlex
  - 2006: Novartis acquired Chiron and Bayer purchased Berlex
  - 2007: Novartis and Bayer finalize agreements that allow Novartis to sell interferon beta-1b under the brand Extavia®
  - Extavia® will have the same production as Betaseron® (e.g., both are manufactured on the same production line and have similar package inserts)

Generic Availability (Federal Trade Commission, Food and Drug Administration)

- Biologic drugs do not have generic equivalents. Congress has introduced legislation to establish regulations to market lower cost generic biologics, also known as follow-on biologics (FOB). Lower-priced FOBs are like generic drugs, but with differences.
- According to the FDA, current technology does not allow for an exact replica of a pioneer biologic drug product. Technology also does not let us conclusively determine whether a FOB product is "interchangeable" with the original branded product such that a patient would be able to switch between the two products without the risk of an adverse effect. Current legislative proposals permit FDA approval of an FOB drug that is sufficiently similar to, but not an exact reproduction of, the original branded biologic product
- FOB products will not be designated as "therapeutically equivalent" with the original biologic drug product.

Comparison to Betaseron

- The differences between the two IFN beta-1b products are the Extavia® brand comes with a 27-gauge needle, packaged with 15 vials for a 30 day supply, while the Betaseron® brand has 30-gauge needles, packaged with 14 vials for a 28 day supply. (Package Inserts)

	EXTAVIA	BETASERON
Compound	IFN beta-1b	IFN beta-1b
Vial Size	Single-use glass vial (3ml)	Single-use glass vial (3 ml)
Needle Size	27-gauge	30-gauge
Units per Pack	15 vials	14 vials
Day Supply	30	28

- Support Programs- Extavia® has a support program run by registered nurses similar to Betaseron's® Betaplus support program.

Table 1: FDA-approved indications for DMDs for MS (Package Inserts)

		Indications			
Drug	**Route**	**Treatment of Relapsing Remitting MS (RRMS)**	**Decrease frequency of clinical exacerbation**	**Slow the accumulation of physical disability**	**Decrease frequency of relapses in RRMS**
IFN beta-1a (Avonex®)	IM	X	X	X	
IFN beta-1a (Rebif®)	SQ	X	X	X	
IFN beta-1b (Betaseron)	SQ	X	X		
IFN beta-1b (Extavia®)	SQ	X	X		
Glatiramer acetate (Copaxone®)	SQ				X

Table 2: Dosing and Administration of DMD for MS (Package Insert)

	IFN beta- 1a (Avonex®)	IFN beta- 1a (Rebif®)	IFN beta- 1b (Extavia®/Betaseron®)	Glatiramer acetate (Copaxone®)
Initial Dose	30 mcg IM weekly	8.8 mcg SC three/wk same time same days (M-W-F) afternoon/evening at least 48 hr apart	0.0625 mg SC every other day	20 mg SC daily
Recommended Titration		Weeks 1-2 8.8 mcg Weeks 2-4 22 mcg Week 5+ 44 mcg	Weeks 1-2 0.0625 mg Weeks 2-4 0.125 mg Weeks 5-6 0.1875 mg Week 7+ 0.25 mg	
Maximum Dose	30 mcg IM weekly	44 mcg SC three/wk	0.25 mg SC every other day	20 mg SC daily
Special Considerations	Pt training on inject	Pt training on inject	Pt training on inject	Pt training on inject
Special populations	Not approved <18 yrs Not studied > 65 yrs	Not approved <18 yrs Not studied > 65 yrs	Not approved <18 yrs Not studied > 65 yrs	Not approved <18 yrs Not studied > 65 yrs
Storage	Refrigerate at 2-8°C	Refrigerate at 2-8°C Can be stored up to 30 days at room temp	Store at room temp. If not injected after mixing, then may refrigerate for 3 hrs	Refrigerate at 2-8°C Can be stored up to 7 days at room temp

Table 3: Interferon Beta-1b Clinical Trial Summaries

Reference Trial Design	Treatments, Concomitant Prophylaxis	Primary Outcome	Results	P value
Study 1 **The IFNB Multiple Sclerosis Study Group 1993** **MC, R, DB, PC** **N=372**	IFN beta-1b 50 mcg SQ EOD (n=111) 250 mcg SQ EOD (n=115) Placebo SQ EOD (n=112) Duration: 2-3 years	Annual exacerbation rate Proportion of exacerbation-free patients	Exacerbation rate Placebo=1.27 50 mcg=1.17 250 mcg=0.84 Exacerbation-Free (# of pts) Placebo =18 50 mcg=23 250 mcg=36	Exacerbation rate P vs. 250 (p=0.0001) 50 vs. 250 (p=0.0086) P vs. 50 (p=0.01) Exacerbation-Free P vs. 250 (p=0.007) 50 vs. 250 (p=0.076) P vs. 50 (p>0.05)
Study 2 **European study Group on IFN beta-1b in Secondary Progressive MS 1998** **MC, DB, R, PC** **N=718**	IFN beta-1b 250 mcg SQ EOD (n=360) Placebo SQ EOD (n=350) Duration: up to 3 years	Progression of disability as measured by EDSS	Significant time delay to disease progression was shown for IFN beta-1b Placebo: 49.7% (178 pts) confirmed progression IFN beta-1b: 38.9% (140 pts) confirmed progression	p=0.0008 p=0.0048 Relative reduction=21.7% in the proportion of pts with progression
Study 3 **The North American Study Group on IFN beta-1b in Secondary Progressive MS 2004** **MC, R, DB, PC**	IFN beta-1b 250 mcg SQ EOD (n=317) 160 mcg/m^2 of BSA SQ EOD (n=314); mean assigned dose=300 mcg Placebo SQ EOD (n=308) Duration: 3 years	Progression of disability as measured by EDSS	Rates of progression did not differ significantly between treatment groups. Secondary measures in the IFN beta-1b group did show improvement involving clinical relapses, newly active MRI lesions, and burden of disease	p>0.05

N=939			measured by MRI.	
BENEFIT trial **Kappos L, et al. 2006** **DB, PC, R, PG , MC, phase III study**	IFN beta-1b 250 mcg SQ EOD (n=292) Placebo SW EOD (n=176) Duration: 2 years	Time to Clinically Definite MS (CDMS) Time to MS according to the McDonald criteria	Hazard Ratio (95%CI) 0.50 (0.36-0.70) 0.54(0.43-0.67) Favoring IFN beta-1b	 p<0.0001 p<0.00001
INCOMIN trial **Durelli, L et al. 2003** **Open label, P, R, PG, MC**	IFN beta-1b 250 mcg SQ EOD (n=92) IFN beta-1a (Avonex) 30 mcg IM q week (n=96) Duration: 2 years	Proportion of patients relapse free Proportion of patients free from new PD/T2 lesions upon MRI	Relapse free- IFN beta-1b 51%, beta- 1a 36% Free of new T2 lesions- IFN beta- 1b 55%, beta-1a 26%	p=0.036 p<0.0003

EOD=every other day, RR=relative reduction, DB=double blind, PC=placebo controlled, R=randomized, PG=parallel group, MC=multicenter, P=prospective

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Place in Therapy (American Academy of Neurology)

- Extavia® holds the same place in therapy as Betaseron®, Avonex®, and Rebif® in treating RRMS.
  - On the basis of several consistent Class I studies, IFN-beta has been demonstrated to reduce the attack rate (whether measured clinically or by magnetic resonance imaging [MRI]) in patients with MS or with clinically isolated syndromes who are at high risk for developing MS
  - It is appropriate to consider IFN-beta for treatment in any patient who is at high risk for developing clinically definite MS (CDMS), or who already has either RRMS or secondary progressive MS (SPMS) and is still experiencing relapses.

Cost Analysis

Drug	Price per vial	Yearly Cost/Pt
Betaseron®	$58.15	$10,467.00
Extavia®	$60.32	$10,857.60

Conclusions

There is no compelling evidence to support the use of IFN beta 1b product over another. The registration trials for Betaseron® were used in the approval of Extavia®. The impact of different needle gauges between the products may influence patient preference, though this has not been evaluated in any clinical trials. The safety profiles for both agents were based on the Betaseron® registry trials.

References

1) Extavia Prescribing Information. Novartis Pharmaceuticals Corporation. East Hanover, NJ. 2009.
2) Novartis Media Release. Basel, Switzerland. March 2007
3) Federal Trade Commission: The Competitive Implications of Generic Biologics, San Fransisco, CA. June 14, 2007
4) U.S. Food and Drug Administration: The Law of Biologic Medicine. June 23, 2004
5) Avonex Prescribing Information. Biogen IDEC Inc. Cambridge, MA. 2006
6) Rebif Prescribing Information. EMD Serono, Inc. Rockland, MA. 2009
7) Betaseron Prescribing Information. Berlex Laboratories. Emeryville, CA. 2003
8) Copaxone Prescribing Information. TEVA Pharmaceuticals USA, Inc., North Wales, PA. 2009
9) Weinstock-Guttman B, Ranshohoff RM, Kinkel RP, et al. The interferons: biological effects mechanisms of action, and use in multiple sclerosis. Ann Neurology. 1995; 37:7-15.

10) Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. American Academy of Neurology - Medical Specialty Society Multiple Sclerosis Council - Disease Specific Society. 2002 Jan 22 (reviewed 2003 Oct). 10 pages. NGC:003144
11) Rice GP, Incorvaia B, Munari LM., Ebers G, Polman C, D'Amico R, Parmelli E, Filippini G. Interferon in relapsing-remitting multiple sclerosis. *Cochrane Database of Systematic Reviews* 2007, Issue 2. Art. No.: CD002002. DOI: 10.1002/14651858.CD002002
12) Study 1: The interferon B Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I Clinical results of a multicenter, randomized, double blind, placebo-controlled trial. Neurology. 1993; 43:655-661.
13) Study 2: The European Study Group on Interferon Beta-1b in Secondary Progressive Multiple Sclerosis. Placebo-controlled multicentre randomized trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet. 1998; 252:1491-97.
14) Study 3: The North American Study Group on Interferon beta-1b in Secondary Progressive MS. Interferon beta-1b in secondary progressive MS. Neurology. 2004; 63:1788-1795.
15) BENEFIT: Kappos L et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology. 2006:67:1242-1249.
16) INCOMIN: Durelli L, Ferrero B, Ghezzi A, et al. The independent comparison of interferon (INCOMIN) trial: a multicenter, randomized trial comparing clinical and MRI efficacy if interferon beta-1a and beta-1b in multiple sclerosis. Neurology. 2002; 56 (supplement 3):148.

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