CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103471Orig1s5186

Trade Name: BETASERON®

Generic or Proper Name: interferon beta-1b

Sponsor: Bayer HealthCare Pharmaceuticals Inc.

Approval Date: 09/25/2015

Indication: BETASERON is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103471/S-5186

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Vicki Chen
Associate Director, Global Regulatory Affairs
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981-0915

Dear Ms. Chen:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received November 25, 2014, submitted under section 351(a) of the Public Health Service Act for Betaseron (interferon beta-1b) Injection.

We acknowledge receipt of your amendments dated January 12, January 15, January 27, February 27, April 10, April 16, May 4, May 29, June 26, July 24, August 26, September 18, and September 23, 2015.

This "Prior Approval" supplemental biologics application provides for the optional use of the BETACONNECT autoinjector for administration of Betaseron.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We remind you that the Bluetooth functionality and system wireless capabilities were not evaluated within this supplemental application. A Prior Approval Supplement will be required before the activation of any functionality or system capabilities that include transmission of patient and/or device use data.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on September 23, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103471/SECONDARY TRACKING NUMBER**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call CDR Hamet Touré, PharmD, Regulatory Project Manager, at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
09/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BETASERON safely and effectively. See full prescribing information for BETASERON.

BETASERON (interferon beta-1b) for injection, for subcutaneous use

Initial U.S. Approval: 1993

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration (2.3) 9/2015

---------- INDICATIONS AND USAGE ----------

BETASERON is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- For subcutaneous use only (2.1)
- The recommended dose is 0.25 mg every other day. Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a six-week period to 0.25 mg (1 mL) every other day. (2.1)
- Reconstitute lyophilized powder with supplied diluent (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

For injection: 0.3 mg of lyophilized powder in a single-use vial for reconstitution (3)

---------- CONTRAINDICATIONS ----------

History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Hepatic Injury* Monitor liver function tests and signs and symptoms of hepatic injury; consider discontinuing BETASERON if serious hepatic injury occurs. (5.1, 5.9)
- *Anaphylaxis and Other Allergic Reactions* Discontinue if anaphylaxis occurs. (5.2)
- *Depression and Suicide* Advise patients to immediately report any symptom of depression and/or suicidal ideation; consider discontinuation of BETASERON if depression occurs. (5.3)
- *Congestive Heart Failure (CHF)* Monitor patients with CHF for worsening of cardiac symptoms; consider discontinuation of BETASERON if worsening of CHF occurs. (5.4)
- *Injection Site Necrosis and Reactions* Do not administer BETASERON into affected area until fully healed; if multiple lesions occur, discontinue BETASERON until healing of skin lesions. (5.5)
- *Leukopenia* Monitor complete blood count. (5.6, 5.9)
- *Flu-like Symptom Complex* Consider analgesics and/or antipyretics on injection days. (5.7)

---------- ADVERSE REACTIONS ----------

In controlled clinical trials, the most common adverse reactions (at least 5% more frequent on BETASERON than on placebo) were: injection site reaction, lymphopenia, flu-like symptoms, myalgia, leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Pregnancy Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide

Revised: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BETASERON (interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose is 0.0625 mg (0.25 mL) subcutaneously every other day, with dose increases over a six-week period to the recommended dose of 0.25 mg (1 mL) every other day (see Table 1).

Table 1: Schedule for Dose Titration

	BETASERON Dose[1]	Percentage of recommended dose	Volume
Weeks 1-2	0.0625 mg	25%	0.25 mL
Weeks 3-4	0.125 mg	50%	0.5 mL
Weeks 5-6	0.1875 mg	75%	0.75 mL
Week 7 and thereafter	0.25 mg	100%	1 mL

1. Dosed every other day, subcutaneously

If a dose of BETASERON is missed, then it should be taken as soon as the patient remembers or is able to take it. The patient should not take BETASERON on two consecutive days. The next injection should be taken about 48 hours (two days) after that dose. If the patient accidentally takes more than their prescribed dose, or takes it on two consecutive days, they should be instructed to call their healthcare provider immediately.

2.2 Reconstitution of the Lyophilized Powder

(a) Prior to reconstitution, verify that the vial containing lyophilized BETASERON is not cracked or damaged. Do not use cracked or damaged vials.

(b) To reconstitute lyophilized BETASERON for injection, attach the pre-filled syringe containing the diluent (Sodium Chloride, 0.54% Solution) to the BETASERON vial using the vial adapter.

(c) Slowly inject 1.2 mL of diluent into the BETASERON vial.

(d) Gently swirl the vial to dissolve the lyophilized powder completely; **do not shake**. Foaming may occur during reconstitution or if the vial is swirled or shaken too vigorously. If foaming occurs, allow the vial to sit undisturbed until the foam settles.

(e) 1 mL of reconstituted BETASERON solution contains 0.25 mg of interferon beta-1b.

(f) After reconstitution, if not used immediately, refrigerate the reconstituted BETASERON solution at 35°F to 46°F (2°C to 8°C) and use within three hours. **Do not freeze**.

2.3 Important Administration Instructions

(a) BETASERON is intended for use under the guidance and supervision of a physician. If patients or caregivers are to administer BETASERON, train them in the proper technique for self-administering

subcutaneous injections using the prefilled syringe or the optional injection device. The BETACONNECT autoinjector has three adjustable injection depth settings; the healthcare provider should determine the proper depth setting and injection technique. Use only the syringes in the BETASERON packaging with the BETACONNECT autoinjector.

The initial BETASERON injection should be performed under the supervision of an appropriately qualified healthcare provider. Users should demonstrate competency in all aspects of the BETASERON injection prior to independent use. If a patient is to self-administer BETASERON, the physical and cognitive ability of that patient to self-administer and properly dispose of syringes should be assessed. Patients with severe neurological deficits should not self-administer injections without assistance from a trained caregiver.

Appropriate instruction for self-injection or injection by another person should be provided to the patient or their caregiver, including careful review of the BETASERON Medication Guide, the prefilled syringe Instructions for Use, and the BETACONNECT autoinjector Instructions for Use that accompanies the product.

(b) Visually inspect the reconstituted BETASERON solution before use; discard if it contains particulate matter or is discolored.

(c) Keeping the syringe and vial adapter in place, turn the assembly over so that the vial is on top. Withdraw the appropriate dose of BETASERON solution. Remove the vial from the vial adapter before injecting BETASERON.

(d) Use safe disposal procedures for needles and syringes.

(e) Do not re-use needles or syringes.

(f) Advise patients and caregivers to rotate sites for subcutaneous injections to minimize the likelihood of severe injection site reactions, including necrosis or localized infection.

2.4 Premedication for Flu-like Symptoms

Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with BETASERON use *[see Warnings and Precautions (5.7)]*.

3 DOSAGE FORMS AND STRENGTHS

For injection: 0.3 mg lyophilized powder in a single-use vial for reconstitution.

4 CONTRAINDICATIONS

BETASERON is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, Albumin (Human), or any other component of the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatic Injury

Severe hepatic injury including cases of hepatic failure, some of which have been due to autoimmune hepatitis, has been rarely reported in patients taking BETASERON. In some cases, these events have occurred in the presence of other drugs or comorbid medical conditions that have been associated with hepatic injury. Consider the potential risk of BETASERON used in combination with known hepatotoxic drugs or other products (eg, alcohol) prior to BETASERON

administration, or when adding new agents to the regimen of patients already on BETASERON. Monitor patients for signs and symptoms of hepatic injury. Consider discontinuing BETASERON if serum transaminase levels significantly increase, or if they are associated with clinical symptoms such as jaundice.

Asymptomatic elevation of serum transaminases is common in patients treated with BETASERON. In controlled clinical trials, elevations of SGPT to greater than five times baseline value were reported in 12% of patients receiving BETASERON (compared to 4% on placebo), and increases of SGOT to greater than five times baseline value were reported in 4% of patients receiving BETASERON (compared to 1% on placebo), leading to dose-reduction or discontinuation of treatment in some patients *[see Adverse Reactions (6.1)]*. Monitor liver function tests *[see Warnings and Precautions (5.9)]*.

5.2 Anaphylaxis and Other Allergic Reactions

Anaphylaxis has been reported as a rare complication of BETASERON use. Other allergic reactions have included dyspnea, bronchospasm, tongue edema, skin rash and urticaria *[see Adverse Reactions (6.1)]*. Discontinue BETASERON if anaphylaxis occurs.

5.3 Depression and Suicide

Depression and suicide have been reported to occur with increased frequency in patients receiving interferon beta products, including BETASERON. Advise patients to report any symptom of depression and/or suicidal ideation to their healthcare provider. If a patient develops depression, discontinuation of BETASERON therapy should be considered.

In randomized controlled clinical trials, there were three suicides and eight suicide attempts among the 1532 patients on BETASERON compared to one suicide and four suicide attempts among 965 patients on placebo.

5.4 Congestive Heart Failure

Monitor patients with pre-existing congestive heart failure (CHF) for worsening of their cardiac condition during initiation of and continued treatment with BETASERON. While beta interferons do not have any known direct-acting cardiac toxicity, cases of CHF, cardiomyopathy, and cardiomyopathy with CHF have been reported in patients without known predisposition to these events, and without other known etiologies being established. In some cases, these events have been temporally related to the administration of BETASERON. Recurrence upon rechallenge was observed in some patients. Consider discontinuation of BETASERON if worsening of CHF occurs with no other etiology.

5.5 Injection Site Necrosis and Reactions

Injection site necrosis (ISN) was reported in 4% of BETASERON-treated patients in controlled clinical trials (compared to 0% on placebo) *[see Adverse Reactions (6.1)]*. Typically, ISN occurs within the first four months of therapy, although postmarketing reports have been received of ISN occurring over one year after initiation of therapy. The necrotic lesions are typically 3 cm or less in diameter, but larger areas have been reported. Generally the necrosis has extended only to subcutaneous fat, but has extended to the fascia overlying muscle. In some lesions where biopsy results are available, vasculitis has been reported. For some lesions, debridement, and/or skin grafting have been required. In most cases healing was associated with scarring.

Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with BETASERON after injection site necrosis has occurred, avoid administration of BETASERON into the affected area until it is fully healed. If multiple lesions occur, discontinue therapy until healing occurs.

Periodically evaluate patient understanding and use of aseptic self-injection techniques and procedures, particularly if injection site necrosis has occurred.

In controlled clinical trials, injection site reactions occurred in 78% of patients receiving BETASERON with injection site necrosis in 4%. Injection site inflammation (42%), injection site pain (16%), injection site hypersensitivity (4%), injection site necrosis (4%), injection site mass (2%), injection site edema (2%) and nonspecific reactions were significantly associated with BETASERON treatment. The incidence of injection site reactions tended to decrease over time. Approximately 69% of patients experienced injection site reactions during the first three months of treatment, compared to approximately 40% at the end of the studies.

5.6 Leukopenia

In controlled clinical trials, leukopenia was reported in 18% of patients receiving BETASERON (compared to 6% on placebo), leading to a reduction of the dose of BETASERON in some patients *[see Adverse Reactions (6.1)]*. Monitoring of complete blood and differential white blood cell counts is recommended. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

5.7 Flu-like Symptom Complex

In controlled clinical trials, the rate of flu-like symptom complex for patients on BETASERON was 57% *[see Adverse Reactions (6.1)]*. The incidence decreased over time, with 10% of patients reporting flu-like symptom complex at the end of the studies. The median duration of flu-like symptom complex in Study 1 was 7.5 days *[see Clinical Studies (14)]*. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with BETASERON use.

5.8 Seizures

Seizures have been temporally associated with the use of beta interferons in clinical trials and postmarketing safety surveillance. It is not known whether these events were related to a primary seizure disorder, the effects of multiple sclerosis alone, the use of beta interferons, other potential precipitants of seizures (eg, fever), or to some combination of these.

5.9 Monitoring for Laboratory Abnormalities

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests, are recommended at regular intervals (one, three, and six months) following introduction of BETASERON therapy, and then periodically thereafter in the absence of clinical symptoms.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more details in other sections of labeling:

- Hepatic Injury *[see Warnings and Precautions (5.1)]*
- Anaphylaxis and Other Allergic Reactions *[see Warnings and Precautions (5.2)]*
- Depression and Suicide *[see Warnings and Precautions (5.3)]*
- Congestive Heart Failure *[see Warnings and Precautions (5.4)]*
- Injection Site Necrosis and Reactions *[see Warnings and Precautions (5.5)]*
- Leukopenia *[see Warnings and Precautions (5.6)]*
- Flu-like Symptom Complex *[see Warnings and Precautions (5.7)]*
- Seizures *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions and over varying lengths of time, adverse reaction rates observed in the clinical trials of BETASERON cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice.

Among 1407 patients with MS treated with BETASERON 0.25 mg every other day (including 1261 patients treated for greater than one year), the most commonly reported adverse reactions (at least 5% more frequent on BETASERON than on placebo) were injection site reaction, lymphopenia, flu-like symptoms, myalgia leukopenia, neutropenia, increased liver enzymes, headache, hypertonia, pain, rash, insomnia, abdominal pain, and asthenia. The most frequently reported adverse reactions resulting in clinical intervention (for example, discontinuation of BETASERON, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were depression, flu-like symptom complex, injection site reactions, leukopenia, increased liver enzymes, asthenia, hypertonia, and myasthenia.

Table 2 enumerates adverse reactions and laboratory abnormalities that occurred among patients treated with 0.25 mg of BETASERON every other day by subcutaneous injection in the pooled placebo-controlled trials (Study 1-4) at an incidence that was at least 2% more than that observed in the placebo-treated patients *[see Clinical Studies (14)]*.

Table 2: Adverse Reactions and Laboratory Abnormalities in Patients with MS in Pooled Studies 1, 2, 3, and 4

Adverse Reaction	Placebo (N=965)	BETASERON (N=1407)
Blood and lymphatic system disorders		
Lymphocytes count decreased (<1500/mm^3)	66%	86%
Absolute neutrophil count decreased (< 1500/mm^3)	5%	13%
White blood cell count decreased (<3000/mm^3)	4%	13%
Lymphadenopathy	3%	6%
Nervous system disorders		
Headache	43%	50%
Insomnia	16%	21%
Incoordination	15%	17%
Vascular disorders		
Hypertension	4%	6%
Respiratory, thoracic and mediastinal disorders		
Dyspnea	3%	6%
Gastrointestinal disorders		
Abdominal pain	11%	16%
Hepatobiliary disorders		
Alanine aminotransferase increased (SGPT > 5 times baseline)	4%	12%
Aspartate aminotransferase increased (SGOT > 5 times baseline)	1%	4%
Skin and subcutaneous tissue disorders		
Rash	15%	21%
Skin disorder	8%	10%
Musculoskeletal and connective tissue disorders		
Hypertonia	33%	40%
Myalgia	14%	23%
Renal and urinary disorders		

Adverse Reaction	Placebo (N=965)	BETASERON (N=1407)
Urinary urgency	8%	11%
Reproductive system and breast disorders		
Metrorrhagia	7%	9%
Impotence	6%	8%
General disorders and administration site conditions		
Injection site reaction[1]	26%	78%
Asthenia	48%	53%
Flu-like symptoms (complex)[2]	37%	57%
Pain	35%	42%
Fever	19%	31%
Chills	9%	21%
Peripheral edema	10%	12%
Chest pain	6%	9%
Malaise	3%	6%
Injection site necrosis	0%	4%

1. "Injection site reaction" comprises all adverse reactions occurring at the injection site (except injection site necrosis), that is, the following terms: injection site reaction, injection site hemorrhage, injection site hypersensitivity, injection site inflammation, injection site mass, injection site pain, injection site edema and injection site atrophy.
2. "Flu-like symptom (complex)" denotes flu syndrome and/or a combination of at least two adverse reactions from fever, chills, myalgia, malaise, sweating.

In addition to the Adverse Reactions listed in Table 2, the following adverse reactions occurred more frequently on BETASERON than on placebo, but with a difference smaller than 2%: alopecia, anxiety, arthralgia, constipation, diarrhea, dizziness, dyspepsia, dysmenorrhea, leg cramps, menorrhagia, myasthenia, nausea, nervousness, palpitations, peripheral vascular disorder, prostatic disorder, tachycardia, urinary frequency, vasodilatation, and weight increase.

Laboratory Abnormalities

In the four clinical trials (Studies 1, 2, 3, and 4), leukopenia was reported in 18% and 6% of patients in BETASERON- and placebo-treated groups, respectively. No patients were withdrawn or dose reduced for neutropenia in Study 1. Three percent (3%) of patients in Studies 2 and 3 experienced leukopenia and were dose-reduced. Other abnormalities included increase of SGPT to greater than five times baseline value (12%), and increase of SGOT to greater than five times baseline value (4%). In Study 1, two patients were dose reduced for increased hepatic enzymes; one continued on treatment and one was ultimately withdrawn. In Studies 2 and 3, 1.5% of BETASERON patients were dose-reduced or interrupted treatment for increased hepatic enzymes. In Study 4, 1.7% of patients were withdrawn from treatment due to increased hepatic enzymes, two of them after a dose reduction. In Studies 1-4, nine (0.6%) patients were withdrawn from treatment with BETASERON for any laboratory abnormality, including four (0.3%) patients following dose reduction.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Serum samples were monitored for the development of antibodies to BETASERON during Study 1. In patients receiving 0.25 mg every other day 56/124 (45%) were found to have serum neutralizing activity at one or more of the time points tested. In Study 4, neutralizing activity was measured every 6 months and at end of study. At individual visits after start of therapy, activity was observed in 17% up to 25% of the BETASERON-treated patients. Such neutralizing activity was measured at least once in 75 (30%) out of 251 BETASERON patients who provided samples during treatment phase; of these, 17 (23%) converted to negative status later in the study. Based on all the available evidence, the relationship between antibody formation and clinical safety or efficacy is not known.

These data reflect the percentage of patients whose test results were considered positive for antibodies to BETASERON using a biological neutralization assay that measures the ability of immune sera to inhibit the production of the interferon-inducible protein, MxA. Neutralization assays are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BETASERON with the incidence of antibodies to other products may be misleading.

Anaphylactic reactions have been reported with the use of BETASERON *[see Warnings and Precautions (5.2)]*.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of BETASERON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: Anemia, Thrombocytopenia

Endocrine disorders: Hypothyroidism, Hyperthyroidism, Thyroid dysfunction

Metabolism and nutrition disorders: Triglyceride increased, Anorexia, Weight decrease, Weight increase

Psychiatric disorders: Anxiety, Confusion, Emotional lability

Nervous system disorders: Convulsion, Dizziness, Psychotic symptoms

Cardiac disorders: Cardiomyopathy, Palpitations, Tachycardia

Vascular disorders: Vasodilatation

Respiratory, thoracic and mediastinal disorders: Bronchospasm

Gastrointestinal disorders: Diarrhea, Nausea, Pancreatitis, Vomiting

Hepatobiliary disorders: Hepatitis, Gamma GT increased

Skin and subcutaneous tissue disorders: Alopecia, Pruritus, Skin discoloration, Urticaria

Musculoskeletal and connective tissue disorders: Arthralgia

Reproductive system and breast disorder: Menorrhagia

General disorders and administration site conditions: Fatal capillary leak syndrome*

*The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of this syndrome.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women; however, spontaneous abortions while on treatment were reported in four patients participating in the BETASERON RRMS clinical trial. BETASERON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When BETASERON (doses ranging from 0.028 to 0.42 mg/kg/day) was administered to pregnant rhesus monkeys throughout the period of organogenesis (gestation days 20 to 70), a dose-related abortifacient effect was observed. The low-effect dose is approximately 3 times the recommended human dose of 0.25 mg on a body surface area (mg/m^2) basis. A no-effect dose for embryo-fetal developmental toxicity in rhesus monkeys was not established.

8.3 Nursing Mothers

It is not known whether BETASERON is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from BETASERON, a decision should be made to either discontinue nursing or discontinue the drug, taking into account the importance of drug to the mother.

8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of BETASERON did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

11 DESCRIPTION

BETASERON (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques. Interferon beta-1b is manufactured by bacterial fermentation of a strain of Escherichia coli that bears a genetically engineered plasmid containing the gene for human interferon $beta_{ser17}$. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

The specific activity of BETASERON is approximately 32 million international units (IU)/mg interferon beta-lb. Each vial contains 0.3 mg of interferon beta-lb. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Mannitol, USP and Albumin (Human), USP (15 mg each/vial) are added as stabilizers.

Lyophilized BETASERON is a sterile, white to off-white powder, for subcutaneous injection after reconstitution with the diluent supplied (Sodium Chloride, 0.54% Solution). Albumin (Human) USP and Mannitol, USP (15 mg each/vial) are added as stabilizers.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of BETASERON (interferon beta-1b) in patients with multiple sclerosis is unknown.

12.2 Pharmacodynamics

Interferons (IFNs) are a family of naturally occurring proteins, produced by eukaryotic cells in response to viral infection and other biologic agents. Three major types of interferons have been defined: type 1 (IFN-alpha, beta, epsilon, kappa and omega), type II (IFN–gamma) and type III (IFN-lambda). Interferon-beta is a member of the type I subset of interferons. The type I interferons have considerably overlapping but also distinct biologic activities. The bioactivities of all IFNs, including IFN-beta, are induced via their binding to specific receptors on the membranes of human cells. Differences in the bioactivities induced by the three major subtypes of IFNs likely reflect differences in the signal transduction pathways induced by signaling through their cognate receptors.

Interferon beta-1b receptor binding induces the expression of proteins that are responsible for the pleiotropic bioactivities of interferon beta-1b. A number of these proteins (including neopterin, β_2-microglobulin, MxA protein, and IL-10) have been measured in blood fractions from BETASERON-treated patients and BETASERON-treated healthy volunteers. Immunomodulatory effects of interferon beta-1b include the enhancement of suppressor T cell activity, reduction of pro-inflammatory cytokine production, down-regulation of antigen presentation, and inhibition of lymphocyte trafficking into the central nervous system. It is not known if these effects play an important role in the observed clinical activity of BETASERON in multiple sclerosis (MS).

12.3 Pharmacokinetics

Because serum concentrations of interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg or less of BETASERON, pharmacokinetic information in patients with MS receiving the recommended dose of BETASERON is not available.

Following single and multiple daily subcutaneous administrations of 0.5 mg BETASERON to healthy volunteers (N=12), serum interferon beta-1b concentrations were generally below 100 IU/mL. Peak serum interferon beta-1b concentrations occurred between one to eight hours, with a mean peak serum interferon concentration of 40 IU/mL. Bioavailability, based on a total dose of 0.5 mg BETASERON given as two subcutaneous injections at different sites, was approximately 50%.

After intravenous administration of BETASERON (0.006 mg to 2 mg), similar pharmacokinetic profiles were obtained from healthy volunteers (N=12) and from patients with diseases other than MS (N=142). In patients receiving single intravenous doses up to 2 mg, increases in serum concentrations were dose proportional. Mean serum clearance values ranged from 9.4 mL/min•kg^{-1} to 28.9 mL/min•kg^{-1} and were independent of dose. Mean terminal elimination half-life values ranged from 8 minutes to 4.3 hours and mean steady-state volume of distribution values ranged from 0.25 L/kg to 2.88 L/kg. Three-times-a-week intravenous dosing for two weeks resulted in no accumulation of interferon beta-1b in sera of patients. Pharmacokinetic parameters after single and multiple intravenous doses of BETASERON were comparable.

Following every other day subcutaneous administration of 0.25 mg BETASERON in healthy volunteers, biologic response marker levels (neopterin, β_2- microglobulin, MxA protein, and the immunosuppressive cytokine, IL-10) increased significantly above baseline six-twelve hours after the first BETASERON dose. Biologic response marker levels peaked between 40 and 124 hours and remained elevated above baseline throughout the seven-day (168-hour) study. The relationship between serum interferon beta-1b levels or induced biologic response marker levels and the clinical effects of interferon beta-1b in multiple sclerosis is unknown.

Drug Interaction Studies

No formal drug interaction studies have been conducted with BETASERON.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

BETASERON has not been tested for its carcinogenic potential in animals.

Mutagenesis

BETASERON was not genotoxic in the in vitro Ames bacterial test or the in vitro chromosomal aberration assay in human peripheral blood lymphocytes. BETASERON treatment of mouse BALBc-3T3 cells did not result in increased transformation frequency in an in vitro model of tumor transformation.

Impairment of Fertility

Administration of BETASERON (doses of up to 0.33 mg/kg/day) to normally cycling female rhesus monkeys had no apparent adverse effects on either menstrual cycle duration or associated hormonal profiles (progesterone and estradiol) when administered over three consecutive menstrual cycles. The highest dose tested is approximately 30 times the recommended human dose of 0.25 mg on a body surface area (mg/m^2) basis. The potential for other effects on fertility or reproductive performance was not evaluated.

14 CLINICAL STUDIES

The clinical effects of BETASERON were studied in four randomized, multicenter, double-blind, placebo-controlled studies in patients with multiple sclerosis (Studies 1, 2, 3, and 4).

Patients with Relapsing-Remitting Multiple Sclerosis

The effectiveness of BETASERON in relapsing-remitting MS (RRMS) was evaluated in a double blind, multiclinic, randomized, parallel, placebo controlled clinical study of two years duration (Study 1). The study enrolled MS patients, aged 18 to 50, who were ambulatory [Kurtzke Expanded Disability Status Scale (EDSS) of ≤ 5.5 – score 5.5 is ambulatory for 100 meters, disability precludes full daily activities], exhibited a relapsing-remitting clinical course, met Poser's criteria for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over two years preceding the trial without exacerbation in the preceding month. The EDSS score is a method of quantifying disability in patients with MS and ranges from 0 (normal neurologic exam) to 10 (death due to MS). Patients who had received prior immunosuppressant therapy were excluded.

An exacerbation was defined as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours.

Patients selected for study were randomized to treatment with either placebo (N=123), 0.05 mg of BETASERON (N=125), or 0.25 mg of BETASERON (N=124) self-administered subcutaneously every other day. Outcome based on the 372 randomized patients was evaluated after two years.

Patients who required more than three 28-day courses of corticosteroids were removed from the study. Minor analgesics (acetaminophen, codeine), antidepressants, and oral baclofen were allowed ad libitum, but chronic nonsteroidal anti-inflammatory drug (NSAID) use was not allowed.

The primary protocol-defined outcome measures were 1) frequency of exacerbations per patient and 2) proportion of exacerbation free patients. A number of secondary clinical and magnetic resonance imaging (MRI) measures were also employed. All patients underwent annual T2 MRI imaging and a subset of 52 patients at one site had MRIs performed every six weeks for assessment of new or expanding lesions.

The study results are shown in Table 3.

Table 3: Two Year RRMS Study Results of Primary and Secondary Clinical Outcomes (Study 1)

Efficacy Parameters		**Treatment Groups**			**Statistical Comparisons p-value**		
Primary End Points		**Placebo (N=123)**	**BETASERON 0.05 mg (N=125)**	**BETASERON 0.25 mg (N=124)**	**Placebo vs 0.05 mg**	**0.05 mg vs 0.25 mg**	**Placebo vs 0.25 mg**
Annual exacerbation rate		1.31	1.14	0.9	0.005	0.113	**0.0001**
Proportion of exacerbation-free patients[1]		16%	18%	25%	0.609	0.288	**0.094**
Exacerbation frequency per patient	0[1]	20%	22%	29%	0.151	0.077	**0.001**
	1	32%	31%	39%			
	2	20%	28%	17%			
	3	15%	15%	14%			
	4	15%	7%	9%			
	> 5	21%	16%	8%			
Secondary Endpoints[2]							
Median number of months to first on-study exacerbation		5	6	9	0.299	0.097	**0.01**
Rate of moderate or severe exacerbations per year		0.47	0.29	0.23	0.02	0.257	**0.001**
Mean number of moderate or severe exacerbation days per patient		44	33	20	0.229	0.064	**0.001**
Mean change in EDSS score[3] at endpoint		0.21	0.21	-0.07	0.995	0.108	**0.144**
Mean change in Scripps score[4] at endpoint		-0.53	-0.5	0.66	0.641	0.051	**0.126**
Median duration in days per exacerbation		36	33	36	ND[5]	ND[5]	**ND[5]**
% change in mean MRI lesion area at endpoint		21.4%	9.8%	-0.9%	0.015	0.019	**0.0001**

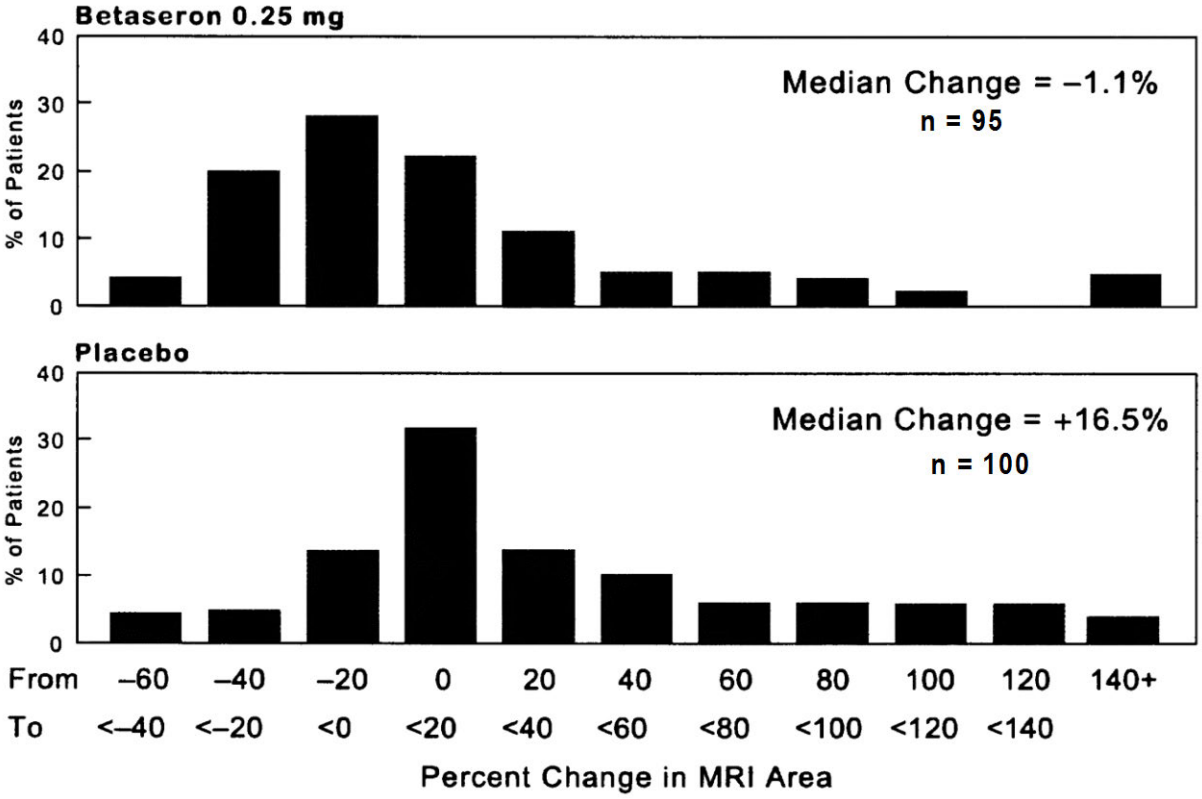
1. 14 exacerbation free patients (0 from placebo, six from 0.05 mg, and eight from 0.25 mg) dropped out of the study before completing six months of therapy. These patients are excluded from this analysis.
2. Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.
3. EDSS scores range from 1-10, with higher scores reflecting greater disability.
4. Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability.
5. ND = Not done.

Of the 372 RRMS patients randomized, 72 (19%) failed to complete two full years on their assigned treatments.

Over the two-year period in Study 1, there were 25 MS-related hospitalizations in the 0.25 mg BETASERON-treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed among the groups, with 16 in the 0.25 mg BETASERON group and 15 in the placebo group. The average number of days of MS-related steroid use was 41 days in the 0.25 mg BETASERON group and 55 days in the placebo group (p=0.004).

MRI data were also analyzed for patients in this study. A frequency distribution of the observed percent changes in MRI area at the end of two years was obtained by grouping the percentages in successive intervals of equal width. Figure 1 displays a histogram of the proportions of patients, which fell into each of these intervals. The median percent change in MRI area for the 0.25 mg group was -1.1%, which was significantly smaller than the 16.5% observed for the placebo group (p=0.0001).

Figure 1: Distribution of Change in MRI Area in Patients with RRMS in Study 1



In an evaluation of frequent MRI scans (every six weeks) on 52 patients at one site in Study 1, the percent of scans with new or expanding lesions was 29% in the placebo group and 6% in the 0.25 mg treatment group (p=0.006).

The exact relationship between MRI findings and clinical status of patients is unknown. Changes in lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in this study has not been evaluated.

Patients with Secondary Progressive Multiple Sclerosis

Studies 2 and 3 were multicenter, randomized, double-blind, placebo controlled trials conducted to assess the effect of BETASERON in patients with secondary progressive MS (SPMS). Study 2 was conducted in Europe and Study 3 was conducted in North America. Both studies enrolled patients with clinically definite or laboratory-supported MS in the secondary progressive phase, and who had evidence of disability progression (both Study 2 and 3) or two relapses (Study 2 only) within the previous two years. Baseline Kurtzke expanded disability status scale (EDSS) scores ranged from 3.0 to 6.5. Patients in Study 2 were randomized to receive BETASERON 0.25 mg (N=360) or placebo (N=358). Patients in Study 3 were randomized to BETASERON 0.25 mg (N=317), BETASERON 0.16 mg/m^2 of body surface area (N=314, mean assigned dose 0.3 mg), or placebo (N=308). Test agents were administered subcutaneously, every other day for three years.

The primary outcome measure was progression of disability, defined as a 1.0 point increase in the EDSS score, or a 0.5 point increase for patients with baseline EDSS $\geq$ 6.0. In Study 2, time to progression in EDSS was longer in the BETASERON treatment group (p=0.005), with estimated annualized rates of progression of 16% and 19% in the BETASERON and placebo groups, respectively. In Study 3, the rates of progression did not differ significantly between treatment groups, with estimated annualized rates of progression of 12%, 14%, and 12% in the BETASERON fixed dose, surface area-adjusted dose, and placebo groups, respectively.

Multiple analyses, including covariate and subset analyses based on sex, age, disease duration, clinical disease activity prior to study enrollment, MRI measures at baseline and early changes in MRI following treatment were evaluated in order to interpret the discordant study results. No demographic or disease-related factors enabled identification of a patient subset where BETASERON treatment was predictably associated with delayed progression of disability.

In Studies 2 and 3, like Study 1, a statistically significant decrease in the incidence of relapses associated with BETASERON treatment was demonstrated. In Study 2, the mean annual relapse rates were 0.42 and 0.63 in the BETASERON and placebo groups, respectively ($p<0.001$). In Study 3, the mean annual relapse rates were 0.16, 0.20, and 0.28, for the fixed dose, surface area-adjusted dose, and placebo groups, respectively ($p<0.02$).

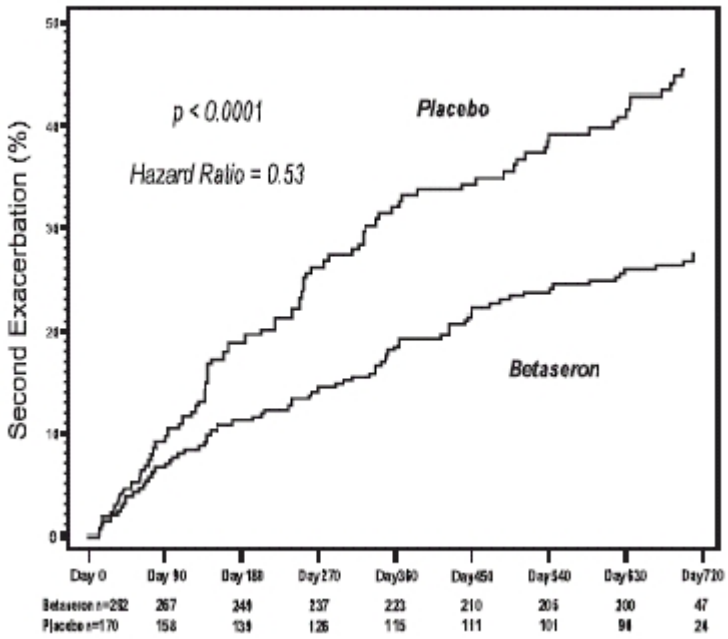
MRI endpoints in both Study 2 and Study 3 showed smaller increases in T2 MRI lesion area and decreased number of active MRI lesions in patients in the BETASERON groups compared to the placebo group. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in MRI findings often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in these studies is not known.

Patients with an Isolated Demyelinating Event and Typical MS Lesions on Brain MRI

In Study 4, 468 patients who had recently (within 60 days) experienced an isolated demyelinating event, and who had lesions typical of multiple sclerosis on brain MRI were randomized to receive either 0.25 mg BETASERON (N=292) or placebo (N=176) subcutaneously every other day (ratio 5:3). The primary outcome measure was time to development of a second exacerbation with involvement of at least two distinct anatomical regions. Secondary outcomes were brain MRI measures, including the cumulative number of newly active lesions, and the absolute change in T2 lesion volume. Patients were followed for up to two years or until they fulfilled the primary endpoint.

Eight percent of subjects on BETASERON and 6% of subjects on placebo withdrew from the study for a reason other than the development of a second exacerbation. Time to development of a second exacerbation was significantly delayed in patients treated with BETASERON compared to patients treated with placebo ($p<0.0001$). The Kaplan-Meier estimates of the percentage of patients developing an exacerbation within 24 months were 45% in the placebo group and 28% of the BETASERON group (Figure 2). The risk for developing a second exacerbation in the BETASERON group was 53% of the risk in the placebo group (Hazard ratio= 0.53; 95% confidence interval 0.39 to 0.73).

Figure 2: Onset of Second Exacerbation by Time in Patients with Isolated Demyelinating Event with Typical MS Lesions on Brain MRI in Study 4*



*Kaplan-Meier Methodology

In Study 4, patients treated with BETASERON demonstrated a lower number of newly active lesions during the course of the study. A significant difference between BETASERON and placebo was not seen in the absolute change in T2 lesion volume during the course of the study.

Safety and efficacy of treatment with BETASERON beyond three years are not known.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BETASERON is supplied as a lyophilized powder in a clear glass, single-use vial (3 mL capacity). Each carton contains 5 single-use cartons (NDC 50419-524-05) or 14 single-use cartons (NDC 50419-524-35).

Each single-use carton contains:

A single-use vial containing 0.3 mg BETASERON (interferon beta-1b)

A pre-filled single-use syringe containing 1.2 mL diluent (Sodium Chloride, 0.54% solution)

A vial adapter with a 30-gauge needle attached

2 alcohol prep pads

The optional BETACONNECT autoinjector is not supplied with BETASERON, but is available for patients with a prescription for BETASERON by calling the BETAPLUS patient support program toll-free number at 1-800-788-1467.

16.2 Stability and Storage

BETASERON and the diluent are for single-use only. Discard unused portions. The reconstituted product contains no preservative. Store BETASERON vials at room temperature 68°F to 77°F (20°C to 25°C). Excursions of 59°F to 86°F (15°C to 30°C) are permitted for up to 3 months. After reconstitution, if not used immediately, refrigerate the reconstituted solution and use within three hours. **Do not freeze.**

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

Instruct patients to carefully read the supplied BETASERON Medication Guide and caution patients not to change the BETASERON dose or schedule of administration without medical consultation.

Instruction on Self-Injection Technique and Procedures

Provide appropriate instruction for reconstitution of BETASERON and methods of self-injection, including careful review of the BETASERON Medication Guide. Instruct patients in the use of aseptic technique when administering BETASERON.

Tell patients not to re-use needles or syringes and instruct patients on safe disposal procedures. Advise patients of the importance of rotating areas of injection with each dose, to minimize the likelihood of severe injection site reactions, including necrosis or localized infection *[see Medication Guide]*.

Hepatic Injury

Advise patients that severe hepatic injury, including hepatic failure, has been reported during the use of BETASERON.

Inform patients of symptoms of hepatic dysfunction, and instruct patients to report them immediately to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Anaphylaxis and Other Allergic Reactions

Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur *[see Warnings and Precautions (5.2)]*.

Depression and Suicide

Advise patients that depression and suicidal ideation have been reported during the use of BETASERON. Inform patients of the symptoms of depression or suicidal ideation, and instruct patients to report them immediately to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Congestive Heart Failure

Advise patients that worsening of pre-existing congestive heart failure have been reported in patients using BETASERON.

Advise patients of symptoms of worsening cardiac condition, and instruct patients to report them immediately to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Injection Site Necrosis and Reactions

Advise patients that injection site reactions occur in most patients treated with BETASERON, and that injection site necrosis may occur at one or multiple sites. Instruct patients to promptly report any break in the skin, which may be associated with blue-black discoloration, swelling, or drainage of fluid from the injection site, prior to continuing their BETASERON therapy *[see Warnings and Precautions (5.5)]*.

Flu-like Symptom Complex

Inform patients that flu-like symptoms are common following initiation of therapy with BETASERON, and that concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with BETASERON use *[see Warnings and Precautions (5.7)* and *Dosage and Administration (2.4)]*.

Seizures

Instruct patients to report seizures immediately to their healthcare provider *[see Warnings and Precautions (5.8)]*.

Pregnancy

Advise patients that BETASERON should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus *[see Use in Special Population (8.1)]*. Therefore, inform patients that if a pregnancy is considered, or does occur, the risks and benefits of continuing BETASERON should be discussed with their healthcare provider.

Medication Guide
BETASERON
(bay-ta-seer-on)
interferon beta-1b
(in-ter-feer-on beta-one-be)

What is the most important information I should know about BETASERON?
BETASERON can cause serious side effects, including:

- **liver problems including liver failure.** Symptoms of liver problems may include:
  - yellowing of your eyes
  - itchy skin
  - nausea or vomiting
  - feeling very tired
  - flu-like symptoms
  - bruising easily or bleeding problems

  Your healthcare provider will do blood tests to check for these problems while you take BETASERON.
- **serious allergic reactions.** Serious allergic reactions can happen quickly and may happen after your first dose of BETASERON or after you have taken BETASERON many times. Symptoms may include difficulty breathing or swallowing, swelling of the mouth or tongue, rash, itching, or skin bumps.
- **depression or suicidal thoughts.** Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:
  - thoughts about suicide or dying
  - new or worse depression
  - new or worse anxiety
  - trouble sleeping (insomnia)
  - acting aggressive, being angry, or violent
  - acting on dangerous impulses
  - hallucinations
  - other unusual changes in behavior or mood

What is BETASERON?
BETASERON is a prescription medicine used to reduce the number of relapses in people with relapsing forms of multiple sclerosis (MS). This includes people who have had their first symptoms of multiple sclerosis and have an MRI consistent with multiple sclerosis. BETASERON is similar to certain interferon proteins that are produced in the body. It will not cure your MS but may decrease the number of flare-ups of the disease.
It is not known if BETASERON is safe and effective in children.

Who should not take BETASERON?
Do not take BETASERON if you are allergic to interferon beta-1b, to another interferon beta, to human albumin, or mannitol. See the end of this leaflet for a complete list of ingredients in BETASERON

What should I tell my healthcare provider before taking BETASERON?
Before you take BETASERON, tell your healthcare provider if you:

- have or have had depression (sinking feeling or sadness), anxiety (feeling uneasy, nervous, or fearful for no reason) or trouble sleeping
- have or have had liver problems
- have or have had blood problems such as bleeding or bruising easily, low red blood cells (anemia) or low white blood cells
- have or have had seizures
- have or have had heart problems
- are pregnant or plan to become pregnant. BETASERON can harm your unborn baby. BETASERON may cause you to lose your baby (miscarry). If you become pregnant while taking BETASERON call your healthcare provider right away. You and your healthcare provider should decide if you should continue to take BETASERON.

- are breastfeeding or plan to breastfeed. It is not known if BETASERON passes into your breast milk. You and your healthcare provider should decide if you will take BETASERON or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take BETASERON?

- See the Instructions for Use at the end of this Medication Guide for complete information on how to use BETASERON.
- BETASERON is given by injection under your skin (subcutaneous injection) every other day.
- Take BETASERON exactly as your healthcare provider tells you to take it.
- If your healthcare provider feels that you or someone else may give you the injections then you or the other person should be trained by your healthcare provider in how to give an injection.
- Do not try to give yourself or have another person give you injections until you or both of you understand and are comfortable with how to prepare your dose and give the injection.
- You may be started on a lower dose when you first start taking BETASERON. Your healthcare provider will tell you what dose of BETASERON to use.
- Your healthcare provider may change your dose of BETASERON. You should not change your dose without talking to your healthcare provider.
- If you miss a dose, you should take your next dose as soon as you remember or are able to take it. Your next injection should be taken about 48 hours (2 days) after that dose. **Do not** take BETASERON on 2 consecutive days. If you accidentally take more than your prescribed dose, or take it on 2 consecutive days, call your healthcare provider right away.
- **Always use a new, unopened vial of BETASERON and pre-filled diluent syringe for each injection.** Throw away any unused medicine. **Do not** re-use any vials, syringes, or needles.
- It is important for you to change your injection site each time you inject BETASERON. This will lessen the chance of you having a serious skin reaction at the site where you inject BETASERON. Avoid injecting BETASERON into an area of skin that is sore, reddened, infected or has other problems.

What are the possible side effects of BETASERON?

BETASERON may cause serious side effects. Call your healthcare provider right away if you have any of the serious side effects of BETASERON including:

- **See "What is the most important information I should know about BETASERON?"**
- **heart problems**. BETASERON may worsen heart problems including congestive heart failure. Symptoms of heart problems may include:
  - swollen ankles
  - shortness of breath
  - not being able to lay flat in bed
  - tightness in chest
  - decreased ability to exercise
  - fast heartbeat
  - increased need to urinate at night
- **injection site problems**. Serious skin reactions can happen in some people including areas of severe damage to skin and the tissue below the skin (necrosis). These reactions can happen anywhere you inject BETASERON. Symptoms of injection site problems may include swelling, redness, or pain at the injection site, fluid drainage from the injection site, and breaks in your skin or blue-black skin discoloration.
- **flu-like symptoms.** BETASERON can cause flu-like symptoms including:
  o fever o tiredness o sweating o chills o muscle aches when you first start to use it
  These symptoms may decrease over time. Taking medicines for fever and pain relief on the days you are using BETASERON may help decrease these symptoms.
- **seizures**. Some people have had seizures while taking BETASERON, including people who have never had seizures before. It is not known if the seizures were related to their MS, to BETASERON, or to a combination of both. If you have a seizure after taking BETASERON call your healthcare provider right away.

The most common side effects of BETASERON include:

o low white blood cell count	o increases in your liver enzymes	o problems sleeping
o headache	o increases in your muscle tension	o weakness
o pain	o rash	o stomach pain

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BETASERON. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BETASERON?

- Before mixing, store BETASERON at room temperature between 68°F to 77°F (20°C to 25°C).
- Before mixing, BETASERON may be stored for up to 3 months between 59°F to 86°F (15°C to 30°C).
- After mixing, you can refrigerate BETASERON for up to 3 hours before using. Your BETASERON must be used within 3 hours of mixing even if refrigerated.
- **Do not freeze.**

Keep BETASERON and all medicines out of the reach of children.
General information about the safe and effective use of BETASERON. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BETASERON for a condition for which it was not prescribed. Do not give BETASERON to other people, even if they have the same symptoms that you have. It may harm them. This Medication Guide summarizes the most important information about BETASERON. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about BETASERON that is written for health professionals. For more information, go to www.BETASERON.com or call BETAPLUS, the BETASERON patient support program, at 1-800-788-1467.
What are the ingredients in BETASERON? **Active ingredient**: interferon beta-1b **Inactive ingredients**: albumin (human), mannitol Diluent contains sodium chloride solution.

Instructions for Use

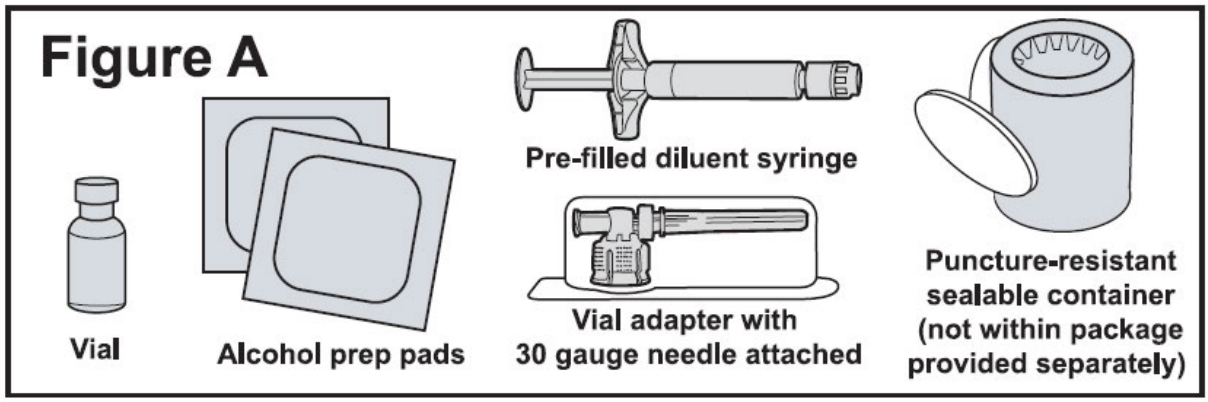
BETASERON
(bay-ta-seer-on)

interferon beta-1b
(in-ter-feer-on beta-one-be)

Read the Instructions for Use that come with your BETASERON before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment. Before you use BETASERON for the first time, make sure your healthcare provider shows you the right way to use it.

Supplies needed for your BETASERON Injection (See Figure A).

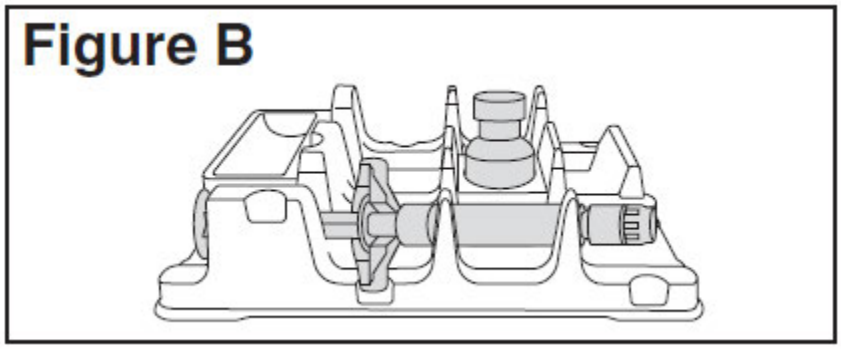
- 1 single-use carton containing:
  - A vial of BETASERON
  - A pre-filled diluent syringe
  - A vial adapter with a 30-gauge needle attached (in the blister pack)
  - 2 alcohol prep pads



Step 1: Preparing for Your BETASERON Injection

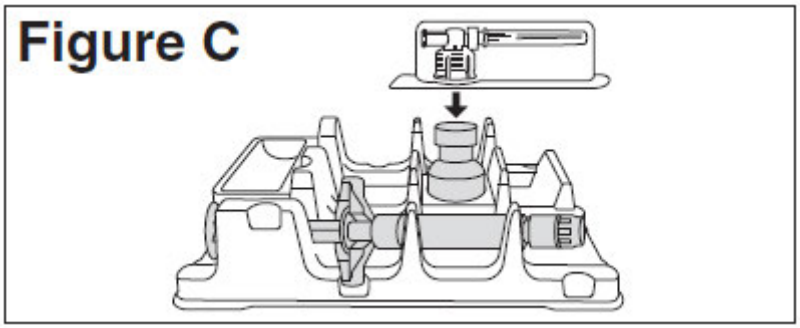
- Place the supplies you will need on a clean, flat surface in a well-lit area.

- Check the expiration date on the single-use carton to make sure that it has not expired. **Do not use it if the medication has expired.**
- Wash your hands thoroughly with soap and water.
- Open the single-use carton and take out all the contents. Make sure the blister pack containing the vial adapter is sealed. Check to make sure the plastic cap on the pre-filled diluent syringe is firmly attached.
- Remove the tray from the single-use carton and place it on a flat surface.
- Place the BETASERON vial in the well (vial holder) and place the pre-filled diluent syringe in the U-shaped trough **(See Figure B).**

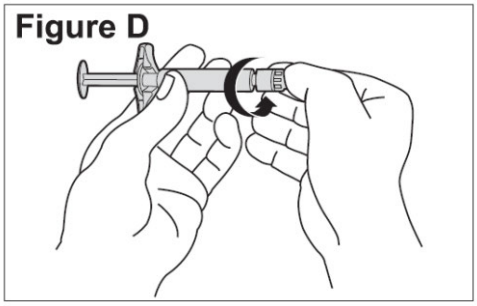


Step 2: Mixing BETASERON

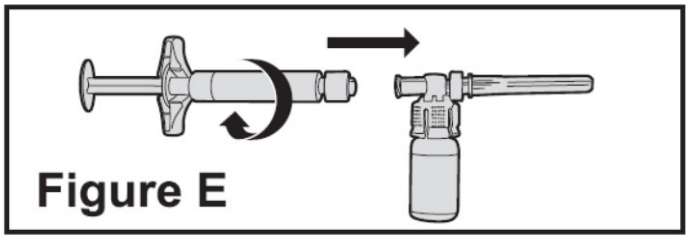
- Remove the BETASERON vial from the well (vial holder) and take the cap off the vial.
- Place the vial back into the well (vial holder).
- Use an alcohol prep pad to clean the top of the vial. Move the alcohol prep pad in 1 direction. Leave the alcohol prep pad on top of the vial.
- Peel the label off the blister pack with the vial adapter in it. The vial adapter is sterile. Do not remove or touch the vial adapter.
- Remove the alcohol prep pad from the top of the BETASERON vial. Pick up the vial adapter in the blister pack. Turn over the blister pack keeping the vial adapter inside. Put the adapter on top of the BETASERON vial. Push down on the adapter until it pierces the rubber top of the BETASERON vial and snaps in place **(See Figure C)**. Remove the blister packaging from the vial adapter.



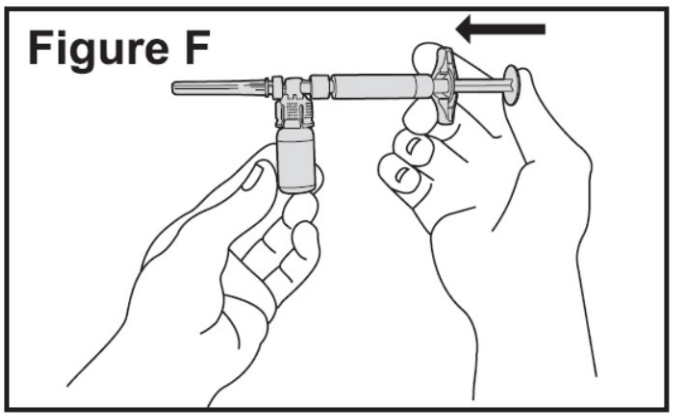
- Twist the plastic cap from the pre-filled diluent syringe. Throw away the plastic cap **(See Figure D)**.



- Keep the vial adapter attached to the vial and remove the vial from the well (vial holder). Be careful not to pull the vial adapter off the top of the vial.
- Connect the pre-filled diluent syringe to the vial adapter by turning clockwise until resistance is felt and the attachment is secure. This forms the syringe assembly **(See Figure E).**



- Slowly push the plunger of the pre-filled diluent syringe all the way in. This will transfer all of the liquid from the syringe into the BETASERON vial **(See Figure F)**. The plunger may return to its original position after you release it.

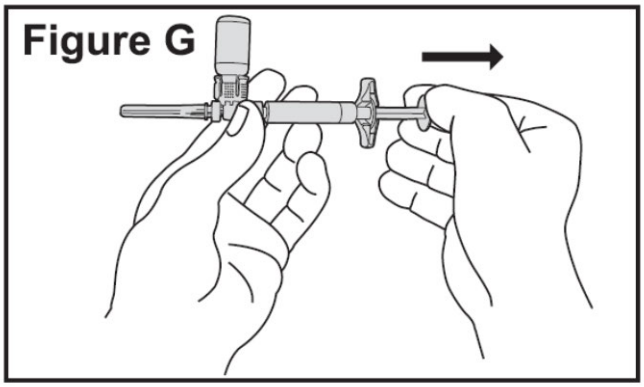


- Gently swirl the vial to completely dissolve the white powder of BETASERON. **Do not shake.** Shaking and even gentle mixing can cause foaming of the medicine. If there is foam, let the vial sit until the foam settles before using it.
- After the powder dissolves, look closely at the solution in the vial. Do not use the solution if it is cloudy or contains particles. It should be clear and colorless.
- Do not use cracked or damaged BETASERON vials. If your vial is cracked or damaged, get a new single-use carton containing a BETASERON vial, pre-filled diluent syringe, vial adapter and 2 alcohol prep pads. Repeat the steps to prepare your BETASERON dose.
- Contact BETAPLUS, the BETASERON patient support program, at 1-800-788-1467 to obtain a replacement product.

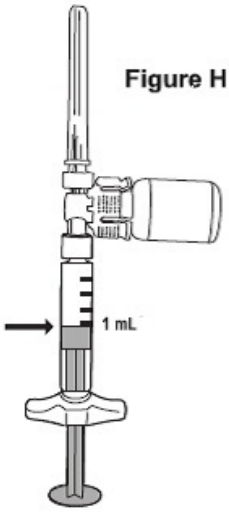
Step 3: Preparing the Injection

You have completed the steps to prepare your BETASERON and are ready for the injection. The injection should be given immediately after mixing and allowing any foam in the solution to settle. If you must wait to give yourself the injection, you may refrigerate the solution and use within 3 hours of mixing your BETASERON. **Do not freeze**.

- Push the plunger in and hold it there; then turn the syringe assembly so that the syringe is horizontal and the vial is on top.
- Slowly pull the plunger back to withdraw all the liquid from the BETASERON vial into the syringe **(See Figure G).**



- NOTE: The syringe barrel is marked with numbers from 0.25 mL to 1 mL **(See Figure H)**. If the solution in the vial cannot be drawn up to the 1 mL mark, discard the vial and syringe and start over with a new single-use carton containing a BETASERON vial, pre-filled diluent syringe, vial adapter and alcohol prep pads.
- Turn the syringe assembly so that the needle end is pointing up. Remove any air bubbles by tapping the outside of the syringe with your fingers. Slowly push the plunger to the 1 mL mark on the syringe or to the mark that matches the amount of BETASERON prescribed by your healthcare provider **(See Figure H).** If too much solution is pushed into the vial, repeat Step 3.



- Turn the syringe assembly so that the vial is at the bottom. Remove the vial adapter and the vial from the syringe by twisting the vial adapter. This will remove the vial adapter and the vial from the syringe, but will leave the needle on the syringe **(See Figure I).**

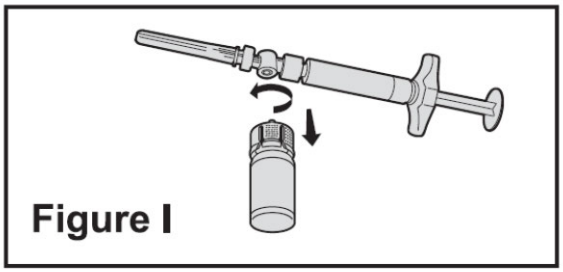


Figure I

Step 4: Choosing an Injection Site

- BETASERON (interferon beta-1b) is injected under the skin and into the fat layer between the skin and the muscles (subcutaneous tissue). The best areas for injection are where the skin is loose and soft and away from the joints, nerves, and bones. **Do not** use the area near your navel or waistline. If you are very thin, use only the thigh or outer surface of the arm for injection.
- Choose a different site each time you give yourself an injection. **Figure J** shows different areas for giving injections**. Do not** inject in the same area for 2 injections in a row. Keep a record of your injections to help make sure you change (rotate) your injection sites. You should decide where you will inject BETASERON before you prepare your medicine for injection. If there are any sites that are difficult for you to reach, you can ask someone who has been trained to give the injection to help you.

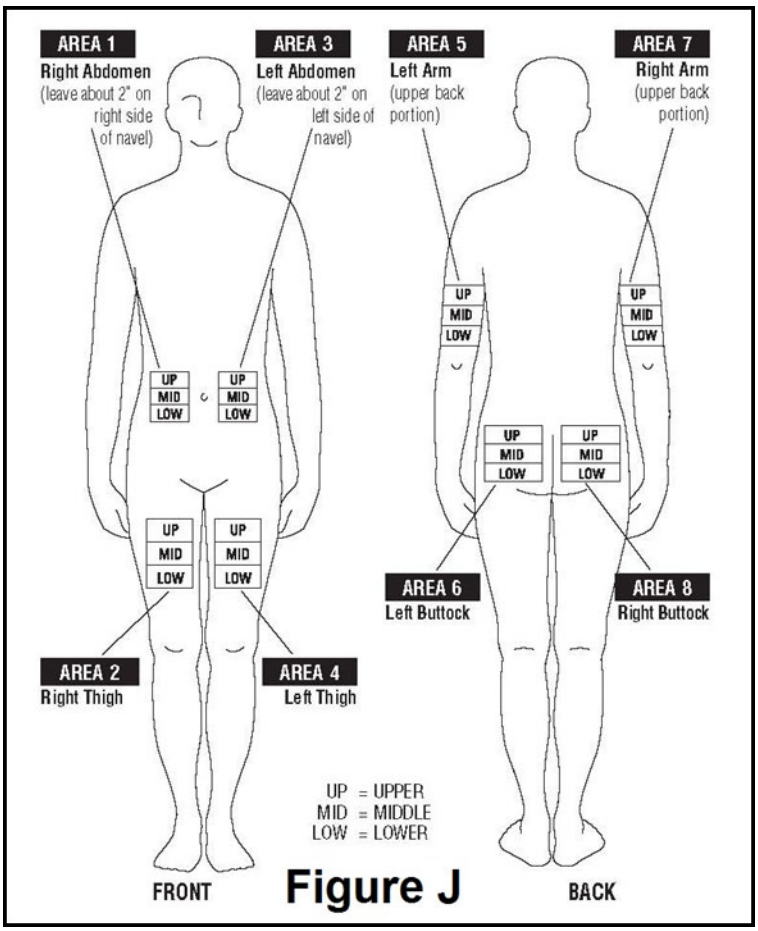
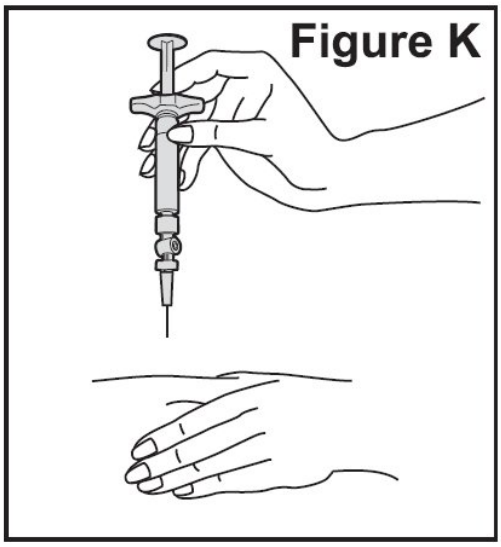


Figure J

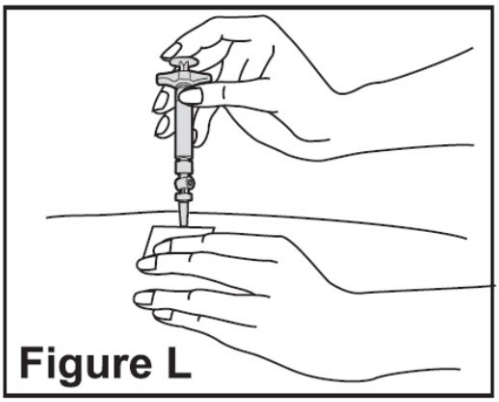
- **Do not** inject BETASERON in a site where the skin is red, bruised, infected, or scabbed, has broken open, or has lumps, bumps, or pain. Tell your healthcare provider if you find skin conditions like the ones mentioned here or any other unusual looking areas where you have been given injections.

Step 5: Injecting BETASERON

- Using a circular motion, clean the injection site with an alcohol prep pad, starting at the injection site and moving outward. Let the skin area air dry.
- Remove the cap from the needle. Hold the syringe like a pencil or dart in 1 hand.
- Gently pinch the skin around the site with the thumb and forefinger of the other hand **(See Figure K).** Insert the needle straight up and down into your skin at a 90° angle with a quick, dart-like motion.



- Slowly push the plunger all the way in until the syringe is empty **(See Figure L).**



- Remove the needle from the skin. Place a dry cotton ball or gauze pad over the injection site. Gently massage the injection site for a few moments with the dry cotton ball or gauze pad. Throw away the syringe in your puncture-proof disposal container.

- Optional Use of BETACONNECT Autoinjector:
  You may also give BETASERON by using the BETACONNECT autoinjector. You should get help with training on the use of the BETACONNECT autoinjector from a healthcare provider before using it for the first time. The BETACONNECT autoinjector should only be used with the syringes that come in the BETASERON packaging. See the Instructions for Use that come with the BETACONNECT autoinjector. For more information, call BETAPLUS, the BETASERON patient support program, at 1-800-788-1467.

Step 6: Disposing of used syringes, needles, and vials

- To prevent needle-stick injury and spread of infection, do not try to re-cap the needle.

- Place used needles, syringes, and vials in a closeable, puncture-resistant container. You may use a sharps container (such as a red biohazard container), hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). Do not use glass or clear plastic containers. Ask your healthcare provider for instructions on the right way to throw away (dispose of) the container. There may be state and local laws about how you should throw away used needles and syringes.
- **Do not throw used needles, syringes, or vials in your household trash or recycle.**
- Throw away any unused medicine. Do not save any unused BETASERON for a future dose.
- Keep the disposal container, needles, syringes, and vials of BETASERON out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration 09/15

Manufactured for:

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

Manufactured in Germany

U.S. License No. 1778

Revision Date: September 2015

BETACONNECT™ autoinjector

Instructions For Use

Language: English

Important Information about your BETACONNECT autoinjector:

- **Only use prepared BETASERON syringes for your injection with the BETACONNECT autoinjector. See the Instructions for Use for BETASERON for how to prepare and measure your dose of BETASERON for use in the BETACONNECT autoinjector.**
- **If this is your first BETASERON injection, it should be given under the supervision of a healthcare provider.**
- **Before you use the BETACONNECT autoinjector for the first time, make sure you get help with appropriate training on its use from a healthcare provider.**

Read these instructions before you use the BETACONNECT autoinjector for the first time. Keep these instructions in a safe place.

Warning!

Whenever you see this symbol it means that safety instructions must be followed.

If you have questions about your BETACONNECT, call BETAPLUS® at 1-800-788-1467 to talk with a BETA Nurse.

- **Do not** use the BETACONNECT if:
  - The prefilled syringe cannot be inserted or removed from the BETACONNECT autoinjector according to the instructions.
  - The syringe was not completely emptied during the last time you tried to use BETACONNECT. (If the injection has been stopped, the syringe will not be completely emptied.)
  - Unexpected events happen, or the BETACONNECT does not operate as described in these Instructions For Use.
- Keep BETACONNECT away from heat or fire. Keep it out of direct sunlight.
- Keep BETACONNECT and its accessories, including cables, out of reach of children. Playing with the cables can lead to strangulation.
- **Do not** use BETACONNECT if, during normal use or during recharging, it does not work as expected or if it appears to be damaged. If this happens, call BETAPLUS at 1-800-788-1467 and speak with a BETA Nurse.
- **Do not** use BETACONNECT in areas with high oxygen levels, such as when supplemental oxygen is in use.
- BETACONNECT is not watertight. Keep it dry. Do not place it in liquid.
- Use your BETACONNECT only with the 30-gauge needles and syringes that come with your BETASERON® (interferon beta-1b).
- Remember that the syringes are made of glass and can break if dropped or hit too hard.
- Only inject into bare skin. **Do not** inject through your clothes.
- To avoid risk of infection, **do not** share your BETACONNECT with another person.
- **Do not** point your BETACONNECT at another person or at yourself except when you are ready to inject.
- Seeing or hearing impaired patients should use BETACONNECT only with the help of a caregiver who is trained to use it.
- Use the built-in reminder only as a backup. You still must take BETASERON on schedule, every other day, and follow the instructions from your healthcare provider even if you use the built-in reminder.
- BETACONNECT is an electronic device. Handle it with care.
- **Do not** change or modify this equipment. **Do not** try to open or repair BETACONNECT. The batteries are not replaceable.
- **Do not** wash BETACONNECT in a dishwasher.
- The safety release is located at the tip of BETACONNECT. It is important to keep the safety release clean. Use a dry or slightly damp cloth or an alcohol wipe.
- If BETACONNECT is exposed to extreme vibration, pressure, or shock (such as being dropped or stepped on), it may be damaged. Check to see that it is working normally.
- BETACONNECT contains rechargeable batteries.
- Use only the charger and cables that came with BETACONNECT. Other cables may create problems or interfere with other electronic devices.
- BETACONNECT cannot be used for injection while charging. Recharge at a temperature between 50°F and 95°F (10°C to 35°C).

Chapter 1: Getting to Know Your BETACONNECT autoinjector

1.1. Getting started

The shipment box contains the following items:

- BETACONNECT™ autoinjector
- Storage case
- Charger
- Micro USB cable
- Quick Start Guide
- BETACONNECT autoinjector Instructions For Use (IFU)

Your BETASERON will arrive in a separate shipment from your pharmacy.

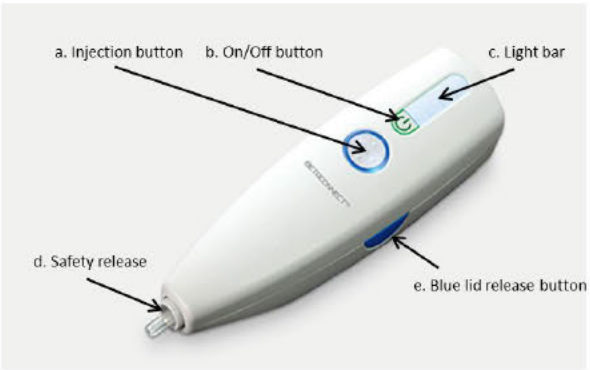
Supplies needed for your BETACONNECT Injection

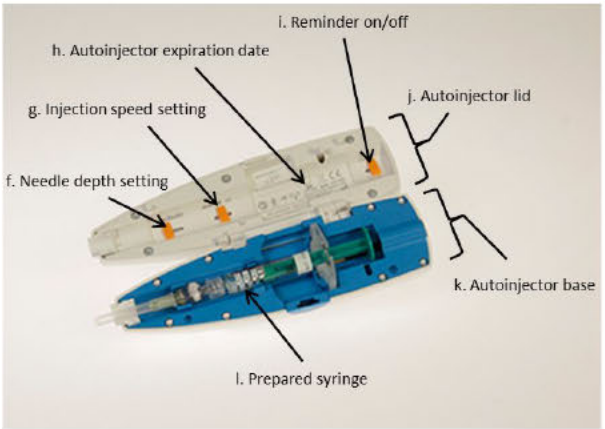
- BETACONNECT autoinjector
- prepared BETASERON syringe with attached capped needle (See Instructions for Use for BETASERON Prefilled Syringe)
- alcohol prep pad
- puncture resistant sharps container for throwing away used needles and syringes. (See "**Disposing of used needles and syringes**" at the end of these Instructions for Use.)

Important: Before you use your BETACONNECT for the first time, you need to charge it fully. Plug the small end of the micro USB cable into your BETACONNECT and the large end into the charger. Plug the charger into a power outlet, and let it charge for about 2 hours. When you see four green bars, BETACONNECT is fully charged.

1.2. Features of your BETACONNECT autoinjector

Check with your healthcare provider before using your BETACONNECT for the first time. Use your BETACONNECT to help you take your BETASERON as prescribed. Remember to change your injection sites each time you inject the medicine as shown in the BETASERON Medication Guide. You will need to prepare the syringe that comes with your BETASERON, and place it in the BETACONNECT autoinjector as shown in the instructions.





a. **Injection button:** Press and release the injection button to start the injection. The injection button flashes blue when the safety is released. There is no need to keep the button pressed during the injection process.
b. **On/off button:** Use the on/off button to turn BETACONNECT on and off. If the on/off button blinks green continuously, or the light bar blinks red, see chapter 5, "Troubleshooting."

c. **Light bar:** Because the injection procedure is quiet, the light bar shows the progress of your injection. BETACONNECT will also sound 2 short beeps and show a blue, flashing bar once the injection is complete and the needle is withdrawn.

d. **Safety release:** When you are ready to inject, activate the safety release by gently holding BETACONNECT against the skin at a 90° angle (straight up and down). It is important to keep the safety release clean.

e. **Blue lid release button:** Use to open the lid.

f. **Needle depth setting:** BETACONNECT allows you to adjust needle insertion depths to 12, 10, or 8 mm. Before making any adjustments, read section 4.1, "Adjusting the injection depth," and talk with your BETA Nurse or healthcare provider.

g. **Injection speed setting:** BETACONNECT allows you to set your injection speed at slow, medium, or fast. Before you make any changes to the speed, read section 4.2, "Adjusting the injection speed."

h. **Autoinjector expiration date:** BETACONNECT comes with an expiration date, to show that the device should not be used after the end of the year (YYYY) and month (MM), printed as YYYY-MM.

i. **Reminder on/off switch:** Use the built-in reminder if you want your BETACONNECT to let you know that it has been 48 hours (2 days) since your last injection. When it is time for your next injection, you should hear a beep and see a flashing light. If you do not want to use the reminder, you can turn it off. See section 4.3, "Setting the injection reminder." Make sure you follow the injection schedule given to you by your healthcare provider.

j. **Autoinjector lid:** You can open the lid by pressing the blue lid release button.

k. **Autoinjector base:** The base is the part of the autoinjector that holds the prepared BETASERON syringe

l. **Prepared syringe:** Use only the syringes that come with your BETASERON. Remember to refer to the BETASERON® (interferon beta-1b) Medication Guide for instructions on how to prepare your syringe. When you insert a prepared syringe, make sure that it is lined up with the syringe outline in the insertion area.

Signals: The BETACONNECT autoinjector:

- Lets you know when it needs recharging. To save battery power, it will automatically power down if not in use for 20 minutes.
- Reminds you when it is time for your next injection with a beep and a flashing light. (If you do not want to use the reminder, you can turn it off using the toggle switch inside the cover.)

1.3. Only use the syringe and 30-gauge needle that come with your BETASERON

BETACONNECT is designed to inject between 0.25 and 1 mL of reconstituted BETASERON, using the syringe and the 30-gauge needle that come with your medicine. Prepare your syringe as shown in the BETASERON Medication Guide. Call BETAPLUS® at **1-800-788-1467** if you need help preparing your injection or have any questions.

Chapter 2: Caring for Your BETACONNECT autoinjector

2.1 Charging your **BETACONNECT**

Important: BETACONNECT must be fully charged before first-time use.

Do not use BETACONNECT while it is charging.

Step 1: Connect the supplied micro-USB cable and charger.

To charge the BETACONNECT autoinjector, plug the micro USB cable into the charger and into your BETACONNECT. Plug the charger into a power outlet, and let it charge for about 2 hours.

A full charge will help make sure that BETACONNECT is ready when you are. A full charge should last for between 15 to 20 injections, or for 4 to 5 weeks.

Step 2: Checking your charge status

4 green bars mean that BETACONNECT is fully charged. After receiving a full charge, your BETACONNECT will turn off.

2.2 Cleaning your **BETACONNECT** autoinjector

- Always store BETACONNECT with the lid closed and in its plastic storage case to help protect it from dust, dirt, extreme temperatures, or direct sunlight.
- It is important to keep the safety release clean. Use a dry or slightly damp cloth or an alcohol wipe.
- If medicine is spilled inside BETACONNECT, remove it right away using a damp cloth.
- Other parts of BETACONNECT do not normally need to be cleaned. If needed, lightly dampen a cloth with water and wipe the device.
- Never place BETACONNECT in any liquid. **Do not** try to clean it in a dishwasher.

Chapter 3: Injecting With Your BETACONNECT autoinjector

Important: Before you use your BETACONNECT for the first time, you need to charge it fully; 4 green bars mean your BETACONNECT is fully charged.

3.1 Preparing your BETACONNECT

Step 1: Turn your BETACONNECT on

Remove the fully charged BETACONNECT from its plastic storage case. Press the on/off button:

- A short beep will tell you that BETACONNECT is turned on.

Wait for the power-on self-test to finish (it takes only a few seconds). When BETACONNECT is ready, the injection button will glow blue and the green light bar will show your charge status.

- If the on/off button blinks green continuously, or the light bar blinks red, see chapter 5, "Troubleshooting."

Step 2: Check your charge

Check the charge status on the light bar:

- 4 green bars indicate that the battery is fully charged.
- If only 1 green bar is flashing, there is enough power for an injection, but the BETACONNECT must be recharged afterwards.
- A flashing orange bar means that the battery level is too low to perform an injection. BETACONNECT will shut off, and you will need to charge it before you can inject.

Step 3: Open the lid

Press the blue lid release button on the side of the BETACONNECT, and fully open the lid.

Important: Remember to refer to the BETASERON® (interferon beta-1b) Medication Guide for instructions on how to prepare your syringe.

Step 4: Insert the syringe into your BETACONNECT

When you have prepared a syringe, leave the needle cap on. Gently fit the syringe into the molded syringe outline in the BETACONNECT autoinjector base until it snaps into place.

- The syringe must be lined up with the syringe outline.
- The lid will not close if the syringe is not seated properly.
- Check that your depth and speed settings are correct. (For depth and speed setting see chapter 4," Making Adjustments.")

Step 5: Close the lid and check the injection button

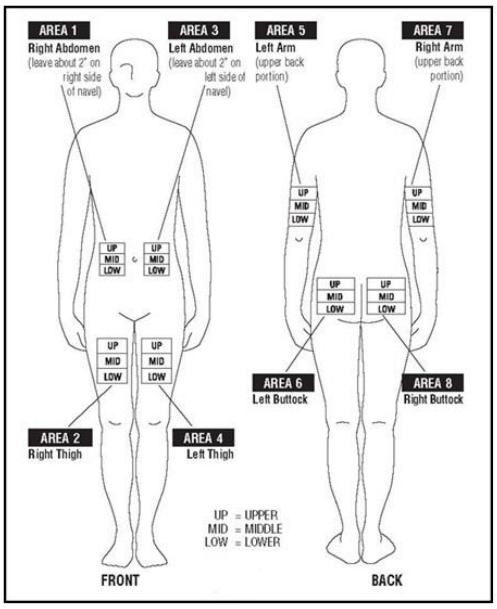
Close the lid. You will hear a click when it shuts.

- When the injection button shows a steady blue light this means that BETACONNECT is now ready to be used for an injection.
- The lid must be fully closed to administer an injection.

3.2 Injection steps

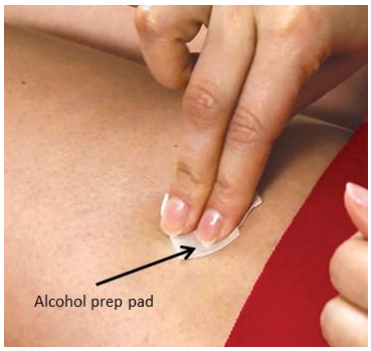
Supplies needed for your BETACONNECT Injection

- BETACONNECT autoinjector
- prepared BETASERON syringe with attached capped needle (See Instructions for Use for BETASERON Prefilled Syringe)
- alcohol prep pad
- puncture resistant sharps container for throwing away used needles and syringes. (See "**Disposing of used needles and syringes"** at the end of these Instructions for Use.)



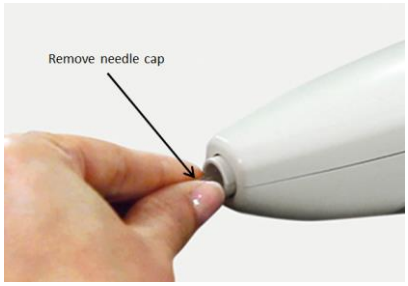
BETASERON is injected under the skin and into the fat layer between the skin and the muscles (subcutaneous tissue). The best areas for injection are where the skin is loose and soft and away from the joints, nerves, and bones such as the stomach (abdomen), upper arm, thigh or buttock. **Do not** use the area near your navel or waistline. If you are very thin, use only the thigh or outer surface of the arm for injection. Choose a different site each time you give yourself an injection. **Do not** inject in the same area for 2 injections in a row.

Step 1: Clean the injection site



Clean the injection site with an alcohol prep pad using a circular motion. Start at the injection site and move outward. Let the skin area air dry.

Step 2: Remove the needle cap



Remove the needle cap by pulling it off at the front of the BETACONNECT. **Do not** twist the needle cap when removing it.

Important: Be careful not to accidentally press the injection button while removing the needle cap

Step 3: Place the BETACONNECT autoinjector against the injection site

Gently hold the BETACONNECT against the skin at a 90° angle (straight up and down) to activate the safety release.

- The injection button flashes blue when the safety is released.
- Make sure you hold the BETACONNECT against your skin for the entire injection.

Important: When BETACONNECT is in “ready” or “inject” mode with a syringe inside, take special care not to accidentally press the injection button.

Step 4: Start the injection

Press and release the injection button to start the injection.

- There is no need to keep the button pressed during the injection process.

Step 5: Check the injection status

The lit blue bar goes down in stages as the injection progresses.

Do not interrupt the injection.
The injection cycle will be interrupted if you:

- Press the on/off button before the injection is complete.
- Remove your BETACONNECT from the injection site before the injection is complete.

If the injection is stopped before your injection is complete you will see a blinking red light.

Check to make sure you received your full dose. If you did not receive your full dose, call your BETA Nurse or healthcare provider.

Important: The injection procedure is quiet. Use the light bar to check the injection status.

Always hold BETACONNECT straight up and down. Keep it pressed against your injection site for as long as the injection lasts.

Step 6: When the injection is finished

BETACONNECT will sound 2 short beeps and show a blue, flashing bar after the injection is complete and the needle is withdrawn.

Do not remove BETACONNECT from the injection site until the injection is complete.

- BETACONNECT will automatically power down once the injection is complete.

3.3 Removing the used syringe and needle

Step 1: Open the lid

Press the blue lid release button on the side of the BETACONNECT, and fully open the lid.

Step 2: Remove the used syringe

Remove the syringe by gently lifting it straight out of the BETACONNECT.

- Hold BETACONNECT with your other hand while removing the syringe. Check the syringe to be sure the entire dose was delivered.

Important: Take care to avoid the needle when you remove the empty syringe. It could injure you or others.

Do not put the needle cap back on the syringe.

Always dispose of your empty syringe promptly, using an appropriate sharps container.

Step 3: Disposing of Used Needles and Syringes

Put your used BETASERON syringe and needle in a FDA-cleared sharps disposal container right away after use.

- **Do not throw away (dispose of) your used syringes and needles in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
    - upright stable during use
    - leak-resistant
    - properly labeled to warn of hazardous waste inside the container
        - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should dispose of used syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
        - Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

        Keep the disposal container out of the reach of children.

Chapter 4: Making Setting Adjustments

4.1. Adjusting the injection depth

Important: Talk with your BETA Nurse or healthcare provider before you change your injection settings.

Step 1: Open the lid fully

Press the blue lid release button to open the lid.

You can set injection depths of 12, 10, or 8 mm by moving the injection depth slider.

When you receive BETACONNECT, it is set to the injection depth of 12 mm. Ask your healthcare provider if you should use a different depth before changing.

Step 2: Set the depth slider to the desired setting

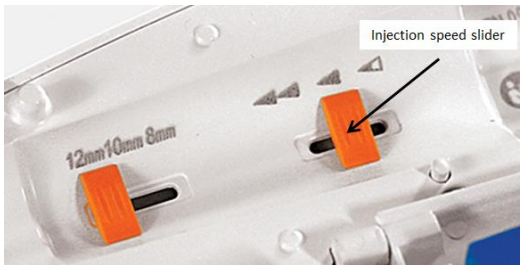
To adjust the injection depth:

12 mm: Move the slider to the 12-mm setting.
10 mm: Move the slider to the 10-mm setting.
8 mm: Move the slider to the 8-mm setting.

4.2. Adjusting the injection speed

Important: Talk with your BETA Nurse or healthcare provider before you change your injection settings.

Step 1: Open the lid fully



Press the blue lid release button to open the lid.

The setting allows for a slow, medium, or fast injection.

When you receive BETACONNECT, it is set to the medium injection speed. Ask your healthcare provider if you should use a different injection setting before changing.

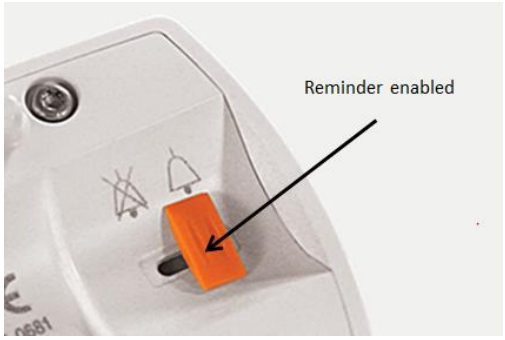
Step 2: Set the injection speed slider to the desired setting

To adjust the injection speed:

Fast: Move slider to ◄◄ symbol.
Medium: Move slider to ◄ symbol.
Slow: Move slider to ◁ symbol.

4.3. Setting the injection reminder

Step 1: Open the lid all the way



Press the blue lid release button to open the lid.

The BETACONNECT will alert you when 48 hours (2 days) have passed since your last injection. The reminder automatically resets after each injection.

When it is time for your next injection, you should hear a beep and see a blue flashing light. The light will flash for 1 hour, and the beep will sound 1 time every 15 minutes for 1 hour.

The reminder is turned on (enabled) when you receive BETACONNECT. If you do not want to use it, you will need to turn it off using the switch shown at left.

- Use the built-in reminder only as a backup. You still must take BETASERON on schedule, every other day, and follow the instructions from your healthcare provider even if you use the built-in reminder.

Step 2: Set the reminder function

To set the reminder:

On, move the slider to

Off, move the slider to

Step 3: When the reminder goes off

Your BETACONNECT will begin to beep and the top of the blue light bar will flash to remind you when it is time to inject.

- The flashing light reminder lasts for 1 hour.
- The beep occurs every 15 minutes for 1 hour.
- You can mute the beep and still have the flashing light reminder by pressing the injection button or opening the lid.
- To cancel both the beep and the flashing light reminder, press the on/off button.

Chapter 5: Troubleshooting

If you need assistance setting up, using, or maintaining your BETACONNECT autoinjector, talk with your BETA Nurse or healthcare provider, or call BETAPLUS® at 1-800-788-1467 anytime.

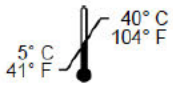
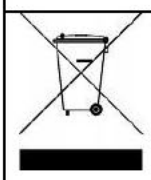
Problem	Cause	Solution
Unable to turn the BETACONNECT autoinjector on by pressing the on/off button	1. On/off button was not pressed long enough.	1. Firmly press the on/off button for more than 2 seconds.
	2. Battery is not charged.	2. Recharge the BETACONNECT autoinjector.
	3. Battery or electronic failure.	3. Contact your BETA Nurse for a replacement.
BETACONNECT autoinjector turns off automatically	1. BETACONNECT autoinjector will automatically turn off after 20 minutes of inactivity.	1. Press the on/off button to turn on.

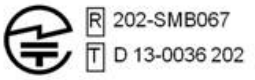
Problem	Cause	Solution
	2. BETACONNECT autoinjector will power off if the battery level is too low.	2. Recharge your BETACONNECT autoinjector if the battery indicator flashes orange when you turn your device on.
Unable to use the BETACONNECT autoinjector while it is being charged	1. The BETACONNECT autoinjector will not operate while it is being charged.	1. Fully charge the BETACONNECT autoinjector and remove the charger before use.
Unable to open the lid	1. The lid cannot be opened during the injection process.	1. Wait until the injection process is completed.
	2. The lid or the blue lid release button does not function.	2. Ask your BETA Nurse or healthcare provider for a replacement.
Unable to inject while the safety release is activated	1. The safety release does not function.	1. Ask your BETA Nurse or healthcare provider for a replacement.
Unable to charge the BETACONNECT autoinjector	1. The wrong micro-USB cable or charger is used.	1. Make sure you use the charger and cables that come with your BETACONNECT autoinjector.
	2. The micro-USB connection is worn out.	2. Ask your BETA Nurse or healthcare provider for a replacement.
Unable to insert the syringe into the BETACONNECT autoinjector	1. The wrong syringe type is used.	1. Use only the syringes that come with your BETASERON.
	2. The syringe is not placed into the insertion area correctly.	2. Make sure that the syringe is lined up with the syringe outline in the insertion area.
	3. The syringe is not prepared correctly.	3. Refer to the instructions in the BETASERON Medication Guide, and prepare a new syringe if necessary.
	4. The plunger is pulled past the 1 mL mark.	4. Adjust the plunger to the 1 mL mark, or the dose prescribed to you by your healthcare provider.
The green light on the on/off button does not stop blinking after the BETACONNECT autoinjector was turned on 	1. The self-test is not completed.	1. Make sure the safety release in the front of the BETACONNECT autoinjector is not pressed.
		2. Open the lid and close the lid. Make sure the lid is fully closed.
		3. Make sure no buttons are pressed down.
		4. Hold the on/off button to shut down BETACONNECT autoinjector, and turn it on again. If the problem is not solved, contact your BETA Nurse or healthcare provider.
A red blinking light is shown on the BETACONNECT autoinjector	1. The injection procedure was interrupted.	1. If the injection was interrupted, check to see that the entire dose was injected. If it was not, talk with your BETA Nurse or healthcare

Problem	Cause	Solution
		provider.
	2. A malfunction was detected.	2. Hold the on/off button down to shut down BETACONNECT autoinjector and turn it on again. If the red blinking light is still there, talk with your BETA Nurse or healthcare provider.
An orange light is shown on the BETACONNECT autoinjector during charging	1. The temperature is too low or too high for charging.	1. The BETACONNECT can be recharged at a temperature from 50°F to 95°F (10°C to 35°C).

6.1 Symbols

The following symbols are used on your BETACONNECT autoinjector and its packaging.

	It is important that you read these instructions before you use the BETACONNECT autoinjector.
	The symbol comes with an expiration date to show that the device should not be used after the end of the year (YYYY) and month (MM), printed as YYYY-MM. Ask your BETA Nurse or Healthcare provider for a replacement.
	Keep your BETACONNECT autoinjector dry.
	The BETACONNECT autoinjector can be **operated** at a temperature from 41°F to 104 °F (5°C to 40°C), at a humidity level of 15% to 93% relative humidity, not condensing, and an atmospheric pressure range of 700 hPa to 1,060 hPa (525 mm Hg to 795 mm Hg).
	The BETACONNECT can be **stored** at a temperature from 14°F to 104 °F (-10°C to 40°C) at a humidity level of 20% to 93% relative humidity, not condensing, and an atmospheric pressure range of 700 hPa to 1,060 hPa (525 mm Hg to 795 mm Hg).
	The BETACONNECT autoinjector contains electrical and electronic components, and must not be disposed of using standard garbage collection. Talk to local authorities about regulations on disposal of electrical and electronic equipment. Follow local regulations for disposal of electronic waste. To protect natural resources and to promote material reuse, separate packaging material from other types of waste, and recycle the material through your local recycling system.

	The BETACONNECT autoinjector is a type BF device, and provides protection against electrical shock and electrical current leakage.
	Manufacturer
	The unique serial number of this BETACONNECT autoinjector.
 0543 0681	The BETACONNECT autoinjector complies with the requirements of The Medical Device Directive (MDD 93/42/EEC), the Radio and Telecommunications Terminal Equipment Directive (R&TTE 1999/5/EC), and the RoHS (Restriction of Hazardous Substances) directive (2011/65/EU).
	The BETACONNECT autoinjector radiates nonionizing electromagnetic signals.
 FCC ID: 2AAGY-BETAC1	This device complies with part 15 of the FCC Rules. Operation is subject to the following 2 conditions: (1) This device may not cause harmful interference, and (2) this device must accept any interference received, including interference that may cause undesired operation.
IC: 3775E-BETAC1	The BETACONNECT autoinjector is IC-authorized under the listed grantee code showing compliance to Canadian regulations regarding unlicensed transmissions. This device complies with Industry Canada license-exempt RSS standard(s). Operation is subject to the following 2 conditions: (1) this device may not cause interference, and (2) this device must accept any interference, including interference that may cause undesired operation of the device.
	Japanese Radio Law and Japanese Telecommunications Business Law Compliance. This device is granted pursuant to the Japanese Radio Law (電波法) and the Japanese Telecommunications Business Law (電気通信事業法). This device should not be modified (otherwise the granted designation number will become invalid).

Expiration and disclaimer

After the expiration date, your BETACONNECT autoinjector has to be replaced. Ask your BETA Nurse or healthcare provider for a new BETACONNECT autoinjector. The expiration date can be located inside the lid indicated by year (YYYY) and month (MM) printed as YYYY-MM. **Do not** use your BETACONNECT autoinjector after the expiration date.

If you have any questions about BETASERON, contact your BETA Nurse at **1-800-788-1467**, or read the Medication Guide and full Prescribing Information for BETASERON.

Talk with your BETA Nurse or healthcare provider:

- If you have any questions about your BETACONNECT
- If you do not need it anymore and want to dispose of it
- If your BETACONNECT does not work the right way or if unexpected events happen.

Manufactured by
Medicom Innovation Partner a/s
Gimsinglundvej 20

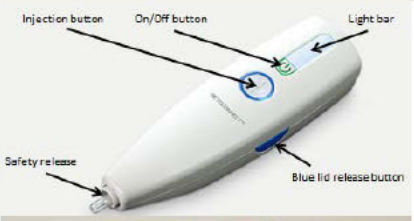
DK-7600 Struer
Denmark

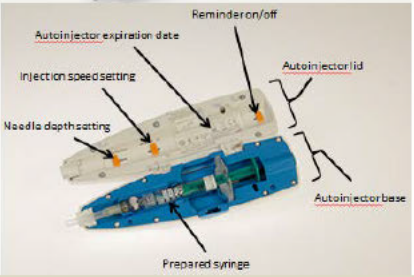
This Instructions for Use has been approved by the U.S. Food and Drug Administration 09/15

BETACONNECT™ autoinjector Quick Guide

Overview

Information: Use only a prepared BETASERON® syringe with attached capped needle.





Injection Process

The injection procedure is quiet. Do not remove BETACONNECT from the injection site until the device has shown that the injection is complete.

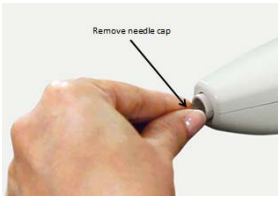
Step 1:
Press the **on/off button** to turn on the BETACONNECT.

Step 2:
Push the blue lid release button to open the lid.

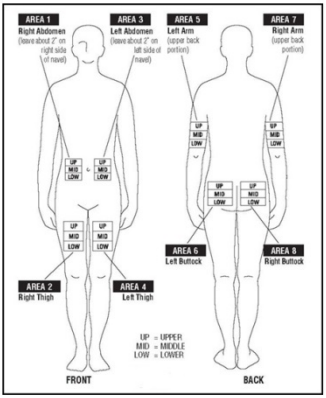
Step 3:
Place the syringe in the BETACONNECT base until it snaps into place.

Step 4:
Close the lid.

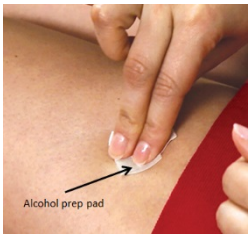
Step 5:
Remove needle cap.



Step 6:
Choose an injection site such as the stomach (abdomen), upper arm, thigh, or buttock. Change the injection site each time you give your injection.



Step 7:
Clean the injection site with an alcohol prep pad using a circular motion starting from the injection site and moving outward. Let the skin dry.



Step 8.
Place the BETACONNECT Autoinjector against the skin at a 90° angle (straight up and down).

Step 9:
Press the injection button to start the injection.

Step 10:
The lit blue bar will go down in stages as the injection progresses. Injection is complete when you hear short beeps and the light bar flashes blue.

Only remove the BETACONNECT from the injection site once the BETACONNECT has

indicated that the injection is complete. Four blue reducing illuminated lights show the injection status. Injection is complete when you hear short beeps and the light bar flashes blue.

Version: 09/15

Manufactured by

Medicom Innovation Partner a/s
Gimsinglundvej 20
DK-7600 Struer
Denmark

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA #/Supplement #	103471/5186
Applicant Name	Bayer HealthCare Pharmaceuticals
Date of Submission	11/25/14
PDUFA Goal Date	9/25/15
Proprietary Name/ Established (USAN) Name	Betaseron/interferon beta-1b
Dosage Forms/Strength	Autoinjector
Proposed Indication(s)	Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager	Hamet Toure, PharmD
Medical Officer Review	Larry Rodichok, MD
Statistical Review	N/A
Pharmacology Toxicology Review	N/A
CMC/OBP Review	Jibril Abdus-Samad, PharmD (OBP labeling)
Microbiology Review	N/A
Clinical Pharmacology Review	N/A
OPDP	Aline Moukhtara, RN, MPH
OSI	N/A
CDTL Review	John Marler, MD
OSE/DMEPA	Justine Harris, RPh
OSE/DDRE	N/A
OSE/DRISK	N/A
OMP/DMPP	Sharon Williams, MSN, BSN, RN
PMHS	N/A
SEALD	N/A
Other	Jason To; Christopher Brown (CDRH)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

Betaseron (interferon beta-1b) is an approved drug product for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

Bayer HealthCare Pharmaceuticals (Bayer) has submitted the current supplemental BLA in order to seek approval for a new Betaseron product that will use an autoinjector as its mechanism of administration. Betaseron, as currently approved, is supplied with syringes prefilled with diluent for injection after reconstitution of lyophilized powder in a vial. The proposed product makes no changes whatsoever to the currently approved Betaseron vials or prefilled syringes. The currently approved prefilled syringe will be used with an optional reusable autoinjector. After preparing the syringe for injection in the usual fashion, the patient can proceed with typical manual injection or can opt to insert the syringe into the autoinjector. The autoinjector will be marketed as Betaconnect and will be available by prescription and provided separately from Betaseron.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

Betaseron was initially approved in 1993. After initial titration, Betaseron is given via conventional subcutaneous injection at a dosage of 0.25 mg every other day. Use with the autoinjector that is the subject of this supplement will not change this dosing regimen.

A pre-sBLA meeting was held with the applicant on September 22, 2014. There are no outstanding issues from that meeting.

3. CMC/Device

As noted above, there are no changes to the currently approved Betaseron drug product. Accordingly, there are no CMC issues.

Mr. To conducted an engineering review of the autoinjector and found that the applicant has provided acceptable information to support its marketing. Mr. To notes that, if approved, the approval letter should note that currently inactive wireless capabilities of the autoinjector were not evaluated and that an additional prior approval supplement should be submitted should the sponsor desire to active those wireless capabilities.

Mr. Brown conducted a compliance review of the autoinjector and found that that application was complete, acceptable, and should be approved. There were no outstanding deficiencies. Mr. Brown recommends a post-approval inspection of the device manufacturing facility, as a pre-approval inspection is not required.

I concur with the recommendations of Mr. To and Mr. Brown and agree with them that there are no device issues precluding approval.

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

N/A

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Ms. Harris reviewed the human factors studies of multiple sclerosis patients and caregivers and identified failures of premature removal of the autoinjector from the injection site. These failures occurred primarily in untrained participants. Therefore, Ms. Harris recommends inclusion of language in labeling indicating that patients should receive training on the use of the autoinjector. No other significant failures were identified and the human factors studies were found to be adequate to support approval. Ms. Harris had several labeling recommendations to promote the safe and effective use of the autoinjector.

I concur with the recommendations of Ms. Harris and agree that there are no outstanding human factors issues that preclude approval.

8. Safety

There were no safety concerns noted in the human factors studies. Dr. Rodichok provided a clinical review to address the adjustable depth setting of the autoinjector. He found no cause for concern in the allowable settings and felt that labeling requiring initial training for patients along with instructions for patients to consult with a healthcare provider before changing the depth setting were acceptable approaches to ensure safe use of the autoinjector.

I concur with the conclusions reached by Dr. Rodichok and Dr. Marler that there are no outstanding safety issues that preclude approval.

9. Advisory Committee Meeting

N/A

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The sponsor has provided adequate information to support the marketing of the Betaconnect autoinjector as an optional mechanism of administration of subcutaneously injected Betaseron. There are no new safety concerns associated with the use of the autoinjector. There are no outstanding unresolved issues.

There are no necessary postmarketing requirements or commitments.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the optional use of the Betaconnect autoinjector with Betaseron to treat relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

For these reasons, I will issue an approval letter for this application, to include the agreed-upon product labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H Dunn
09/25/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Betaconnect Autoinjector for Betaseron - Labeling Supplement

Date	September 11, 2015
Reviewer	John Marler, MD
Subject	Cross-Discipline Team Leader Review
NDA	BLA 103471, Supplement 5186
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	November 25, 2014
Type of Submission	Prior approval supplement. Efficacy labeling change with clinical data.
Sponsor's Document Sequence Numbers	eCTD 0136 through 0146 SDN 1035 to 1071
PDUFA Goal Date	November 25, 2014
Proprietary Name / Established (USAN) names	BetaConnect Autoinjector for use with Betaseron pre-filled syringe
Dose Regimen	The recommended starting dose is 0.0625 mg (0.25 mL) subcutaneously every other day, with dose increases over a six week period to the recommended dose of 0.25 mg (1 mL) every other day
Dosage forms / Strength	0.3 mg of lyophilized powder in a single-use vial for reconstitution using a syringe pre-filled with diluent. Betaconnect is an optional autoinjector prescribed for use with the Betaseron pre-filled syringe.
Proposed Indication(s)	Relapsing Multiple Sclerosis
Recommended:	Approval of Betaconnect autoinjector

1. Introduction

This cross-discipline team leader review recommends approval of a labeling supplement that adds the Betaconnect electronic autoinjector to the labeling for Betaseron interferon β-1b. There are no changes to the Betaseron drug product. The review team (see Table 1) assessed the quality of the Betaconnect device engineering and manufacturing, the usability by patients and caretakers, the safety of the device, and the accuracy of the labeling for the constituents of the combination product. The team found no problems that precluded approval. Issues that the team discussed included disabling of the wireless capabilities of the Betaconnect device, the settings for injection depth, and the extent to which Betaseron labeling would describe the availability of Betaconnect autoinjector. All the issues have been resolved.

Table 1 List of Review Team Members Noting Those Who Filed Reviews

Discipline	Reviewer	TL	Review
OBP	Ralph Bernstein	Cristina Ausin	Yes
OBP	Jibril Abdus-Samad		
DNP Clinical (Division of Neurology Products)	Larry Rodichok	John Marler	Yes
CDRH (Office of Device Evaluation)	Jason To	Alan Stevens	Yes
Combination Products		Patricia Love	
Office of Process and Facilities	Steven Fong		
CDRH (Compliance)	Christopher Brown		
CDRH (Office of Compliance)	Crystal Lewis		
OSE RPM	Ermias Zerislassie	Darrell Jenkins	
DMEPA	Justine Harris	Danielle Harris	Yes
DMPP Patient Labeling (Med Guide PPI)	Sharon Williams		
OPDP (Prescribing Information and Med	Aline Moukhtara	Mathilda Fienkeng	
Labeling	Nicole Bradley and Tracy Peters		
RPM	Hamet Touré	Jackie Ware	

2. Background

Drug Product

FDA approved Betaseron for treating relapsing forms of multiple sclerosis in 1993. Bayer provides the drug as a lyophilized powder in a vial. A co-packaged pre-filled syringe contains diluent for reconstitution by injection into the vial. The patient or care provider draws reconstituted drug from the vial back into the syringe for subcutaneous injection. The dosage is 0.25 mg interferon-β-1b in 1.0 mL delivered subcutaneously every other day. For first use, the starting dose is 0.0625mg. The starting dose increases in steps to the full 0.25mg dose over 8 weeks.

Betaconnect Autoinjector Device

The Betaconnect device is an electronic re-usable autoinjector designed for use with the same disposable pre-filled piston syringes that the manufacturer provides with the current Betaseron drug product. After preparing the syringe for injection, the patient can use it immediately for manual injection or insert the syringe into the Betaconnect autoinjector for automatic injection. The autoinjector functions are needle insertion, drug injection, post injection hold, and needle retraction as well as optional visual and acoustic reminders. There are three injection depth settings (12, 10, and 8 millimeters) and three injection speed settings that users may select. The proposed instructions for use (IFU) require the patient to change the depth setting only under the supervision of a health care provider.

Betaconnect will be available by prescription only. The sponsor will distribute Betaconnect separately from the Betaseron product. The following items are included with the Betaconnect: storage case, USB cable, USB wall charger, Instructions for Use (IFU) and Quick Guide.

The injection speed and depth settings are in the interior compartment of Betaconnect. Users have to slide a button to change the setting while the lid is open. The sponsor states, and DMEPA reviewers agree, that it is unlikely users will accidently change the settings even when the lid is open.

Other interferon-β products administered by injection for multiple sclerosis

Since the approval of Betaseron in 1993, FDA has approved Avonex, Rebif, and Extavia. The drug substance for Avonex and Rebif is interferon-β-1a. Extavia is the same drug product as Betaseron. Patients self-administer Rebif subcutaneously with single-use prefilled syringes or single-use pre-filled autoinjectors. Rebif does not require reconstitution. The Dosage and Administration section of the Rebif label provides the following "Important Administration Instructions":

> REBIF is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections using the prefilled syringe or injection device approved for use with REBIF. Injection depth of the REBIF Rebidose autoinjector is fixed at 8 mm; the healthcare provider should determine the injection technique.
>
> The initial injection should be performed under the supervision of an appropriately qualified healthcare provider.
>
> Appropriate instruction for self-injection or injection by another person should be provided to the patient or their caregiver, including careful review of the REBIF Medication Guide and the REBIF Rebidose autoinjector Instructions for Use that accompanies the product. Users should demonstrate competency in all aspects of the injection prior to independent use. If a patient is to self-administer REBIF, the physical and cognitive ability of that patient to self-administer and properly dispose of prefilled syringes or the REBIF Rebidose autoinjectors should be assessed. Patients with severe neurological deficits should not self-administer injections without assistance from a trained caregiver.

Avonex requires intramuscular injection. Patients self-administer Avonex using single use prefilled syringes or single use pre-filled autoinjectors. Pertinent excerpts from Avonex labeling include:

> The first AVONEX injection should be performed under the supervision of an appropriately qualified healthcare professional. If patients or caregivers are to administer AVONEX, train them in the proper intramuscular injection technique and assess their ability to inject intramuscularly to ensure the proper administration of AVONEX.
>
> A 25 gauge, 1" needle for intramuscular injection with AVONEX prefilled syringe or injection of reconstituted solution may be substituted for the 23 gauge, 1 ¼" needle by the healthcare provider, if deemed appropriate. A 25 gauge, 5/8" needle specific to the prefilled autoinjector is supplied with the AVONEX PEN® Administration Dose Pack. DO NOT use any other needle with the autoinjector.

It is clear that consistency with other injectable MS interferon products requires instructions in the Betaseron label for a health care professional to train the patient and supervise the first Betaconnect injection.

Regulatory background

The review team met with the sponsor at a pre-sBLA meeting on September 22, 2014, to discuss the sponsor's plans to market a separately distributed electronic autoinjector [Betaconnect] with instructions for use that refer to a mobile telephone application [myBETAapp] that communicates wirelessly with the autoinjector and

(b) (4)

Items of discussion included the human factors studies, labeling changes, the nature of the combination product, and the need for prior approval of the supplement.

In a post-meeting comment in the minutes[1] FDA agreed that if BetaConnect is in a separate package, the packaging should contain the BetaConnect Instructions for Use but that FDA would determine the extent to which the Betaseron package insert should contain instructions for BetaConnect. FDA stated that the Betaseron prescribing information should identify all constituent parts of the combination product as a whole but agreed it might be feasible to indicate the location of the instruction details rather than provide the full Betaconnect instructions in the Betaseron prescribing information. The review team has now agreed that this is a reasonable approach and recommends that the sponsor package the Betaconnect device instructions separated from the Betaseron drug packaging in the packaging for the device.

At the pre-BLA meeting, FDA referred the sponsor to the Office of Combination Products for discussion of the extent to which the sponsor must describe the software

[1] Meeting Minutes, sent to sponsor 10-19-2015.
http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8035e312

in the combination product label. FDA informed Bayer that the myBETAapp (b) (4) applications are device constituent parts of the combination product and regulated as part of the entire combination product system. After discussions with the Office of Combination Products after the pre-BLA meeting and prior to submission of this supplement, the sponsor (b) (4)

3. CMC/Device

The Office of Biotechnology Products review team consisted of Ralph Bernstein, Jibril Abdus-Samad, and Cristina Ausin. They determined that there is no change in drug-product container closure contact and no effect on drug-product quality. They identified no issues that would prevent approval of the Betaconnect autoinjector.

4. CDRH Combination Product Consult

Jason To, Alan Shepherd, Christopher Brown, and Cristal Lewis prepared the CDRH responses to a DNP request for consultation regarding the approvability of the Betaconnect autoinjector device used with a prepared Betaseron pre-filled syringe. The CDRH review concludes that there are sufficient data to support the marketing of the Betaconnect autoinjector device constituent of the combination product.

The CDRH conclusion does not apply to the Betaconnect wireless capabilities. CDRH recommends that the approval letter state that FDA did not evaluate the Bluetooth functionality and system wireless capabilities of the Betaconnect autoinjector and that CDER require a prior approval supplement before activation of any system capabilities that transmit data related to the patient or the use of the device. The review also describes CDRH concerns about the use of the name "Betaconnect" for an auto-injector that does not have its wireless connectivity functionality enabled. DMEPA granted conditional approval for the Betaconnect name after considering the CDRH concerns that the "connect" in the name implied that the device wireless capability was functional.[2]

CDRH reviewed injection depth accuracy. Betaconnect allows users to select injection depth setting after consultation with a qualified healthcare provider. The 3 injection depth settings for Betaconnect are 8mm ((b) (4)), 10mm (b) (4), and 12mm (b) (4)

[2] "Proprietary Name Request Conditionally Acceptable" Letter signed by Todd Bridges, DMEPA, July 8, 2015.

(b) (4)). Test results for depth provided (b) (4) confidence that the design will operate within a range of (b) (4), (b) (4), and (b) (4).

The device label states (b) (4) because (b) (4) of the Betaconnect devices fail after full immersion in water. The CDRH team does not consider the failure after immersion to be a reason for disapproval because the failure would be apparent to the patient and the patient could use the prepared syringe to complete a manual injection without the Betaconnect autoinjector.

CDRH confirmed that the wireless capabilities of the Betaconnect device would not function in the United States. Patients in the U.S. who (b) (4)

Lening Shen, software engineer, and Jessica Eisner, MD, had no concerns regarding the device software for the reminder function. They noted that failure could result in a missed dose and recommended labeling changes to advise the patient of the limitations of the reminder system.

5. DMEPA Review of Human Factors Studies

Justine Harris, RPh, wrote the DMEPA review in collaboration with Quynh Nhu Nguyen, MS, human factors specialist, Danielle Harris, PharmD, team leader, and Irene Chan, Associate Director. The review requests labeling changes to address concerns about injection depth, instructions for use, and references to (b) (4) before the supplement is approved.

The DMEPA review notes that the human factors studies did not assess injection site selection. However, DMEPA agrees that the Betaseron IFU adequately describes this task and has no concerns that the addition of Betaconnect as an optional injection method would alter the process for injection site selection. I would add that this does not mean that all the sites suitable for manual injection would be suitable for Betaconnect. My interpretation is that the choice of injection sites depends also on instructions and training by a healthcare professional. This concept will guide changes in the sponsor's proposed label during the discussions of the label.

The sponsor's human factors studies also did not assess the users' ability to perform adjustments to the injection speed and injection depth settings. DMEPA accepts

Bayer's rationale for not testing the use of these settings: speed and depth are optional settings primarily designed for patient comfort. DMEPA was also reassured because the Betaconnect IFU contains statements instructing patients to check first with the MS nurse or healthcare provider prior to changing the depth or speed settings. DMEPA agrees that changes to the Betaseron prescribing information Dosage and Administration Section would address concerns about patient errors setting the depth and speed. DMEPA determined that these label changes would not require another human factor validation study.

DMEPA review of the human factors study report showed acceptable results with the exception of the failures of removing the autoinjector from the injection site prematurely. However, these failures primarily occurred with untrained participants. Therefore, DMEPA recommends that the Betaconnect carton labeling and prescribing information require instruction from a healthcare provider before first use. As part of the instruction, DMEPA recommends that labeling require that a qualified healthcare professional supervise a patient's first BETASERON injection using Betaconnect.

6. Nonclinical Pharmacology and Toxicology

The submission contained no material for review by the nonclinical pharmacology and toxicology team.

7. Clinical Pharmacology

The submission contained no material for review by the clinical pharmacology review team.

8. Clinical Microbiology

The submission contained no material for review by the clinical microbiology review team.

9. Clinical/Statistical - Efficacy

The submission does not contain efficacy data. The Division of Medication Errors and Prevention (DMEPA) reviewed the clinical data from human factors studies of the usability of the autoinjector device. Larry Rodichok, MD, provided a short review in response to questions from the DMEPA team regarding possible concerns about the selection of injection depth. His review cites a source also referenced by the sponsor

that suggests there is wide variation in the thickness of subcutaneous tissue.[3] My interpretation of the article is that the thickness of the subcutaneous tissue varies widely in the same individual and between individuals. It is unlikely any fixed needle length could work at most potential injection sites in most patients. With adequate instruction and oversight of depth adjustments, providers can train patients to inject into sites with adequately deep subcutaneous tissue. The current needle length used for manual injections is longer than the maximum Betaconnect injection depth. Dr. Rodichok is reassured by the proposed labeling that states that the patient must consult a healthcare before changing the depth setting. Dr. Rodichok concludes that it is reasonable to assume that a trained healthcare professional is competent to choose an appropriate depth setting for an individual patient.

10. Safety

The submission contained no material for clinical safety data for review.

11. Advisory Committee Meeting

There was no advisory committee meeting for this submission.

12. Pediatrics

Not applicable.

13. Other Relevant Regulatory Issues

None.

14. Labeling

At the time of this review, the labeling is still under discussion by the review team and negotiation with the sponsor is pending. The key labeling changes relate to references in the prescribing information to the instructions for use packaged separately with Betaconnect, a requirement for instruction and first-dose supervision by a healthcare professional, and setting the depth of the injection. CDRH recommended changing instructions for use to state that "The BetaConnect reminder function is only intended as a supplement to your current reminder system."

[3] Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Current Medical Research & Opinion (2010; 26(6): 1519-1530).

15. CDTL Recommendations/Risk Benefit Assessment

I recommend approval for the Betaconnect autoinjector combination product. The device has met CDRH engineering standards and meets usability-testing standards as reviewed by DMEPA. The review team carefully considered the issues related to depth of injection. Because of wide variation among individuals in the depth of subcutaneous tissue at potential injection sites, successful injection depends on health care professionals to determine appropriate sites and depths of injection for each individual and provide individual training. This issue is not unique to autoinjectors or to the Betaseron product. To the extent possible, the label changes for the Betaconnect autoinjector will be consistent with the labeling for autoinjectors for other interferons. In my opinion, these measures will likely maintain risk levels similar to those attainable with the current pre-filled Betaseron syringe as used for manual injection where the needle length exceeds the maximum injection depth available using the same syringe with Betaconnect.

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/s/

JOHN R MARLER
09/11/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
Review of labelling supplement

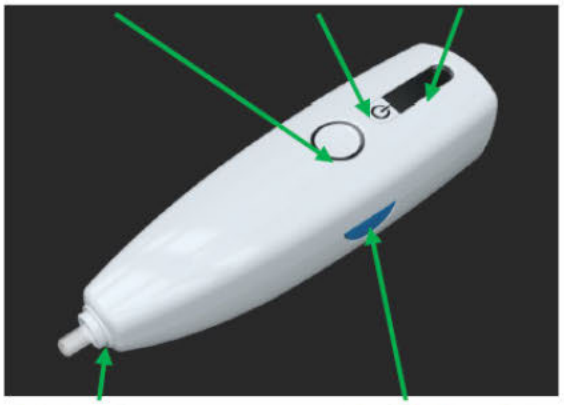
BLA	103471 Supplement 5186
Supporting Document Number:	1035; e0136 to 0146
Sponsor:	Bayer HealthCare
Drug:	Betaseron™ BetaConnect autoinjector
Proposed Indication:	Use of BetaConnect Autoinjector
Correspondence Date:	1/12/15 through 7/24/15
Date Received / Agency:	1/12/15 through 7/24/15
Date Review Completed	8/25/15
Reviewer:	Lawrence Rodichok MD, ODEI, DNP
Materials Reviewed	Clinical information related to the use of the BetaConnect autoinjector

FDA text, *reviewer comment*, extracted from sponsor documents

1. Executive Summary

1.1. Product introduction

The BETACONNECT device is a reusable electronic autoinjector that is intended for use with pre-filled syringes of Betaseron. The device would be on option to the use of the pre-filled syringe for manual injection.



The device is intended for use with pre-filled syringes only.

The device does include adjustable depth and speed of injection settings. The sponsor proposed to only refer to the autoinjector in the Betaseron label. Instructions for use (IFU or the device "label") are provided separately.

1.2. Review of clinical information

The sponsor has provided a human factors study which is general shows satisfactory results. This study did not include information on the use of the adjustable depth or speed of injection settings. The available injection depth settings (8, 10 and 12mm) may result in an intramuscular (IM) injection depending on the thickness of the subcutaneous layer and the site of injection (Gibney et al., 2010). The sponsor proposes to include in the instructions for use (IFU) a warning to patients that these settings should not be altered without consulting a health care provider, i.e. the physician prescribing the device or their designee. It is reasonable to assume that the prescriber is competent to choose the appropriate depth setting. No adverse consequences other than patient discomfort are expected should the injection be IM instead of the intended subcutaneous route of administration.

From the proposed IFU:

h. Needle depth setting: BETACONNECT [redacted] (b) (4) allows you to adjust needle insertion depths to 12, 10, or 8 mm. Before making any adjustments, please read section 4.1, "Adjusting the injection depth," and talk with your BETA Nurse or healthcare provider.

4.1. Adjusting the injection depth

Important: Talk with your BETA Nurse or healthcare provider before you change your injection settings.

Step 1: Open the lid fully

Press the blue lid release button to open the lid.

You can set injection depths of 12, 10, or 8 mm by moving the injection depth slider.

By default, BETACONNECT Autoinjector is set to the injection depth of 12 mm. Ask your healthcare provider if you should use a different depth before changing.

Step 2: Set the depth slider to the desired setting

To adjust the injection depth:

12 mm: Move the slider to the 12-mm setting.
10 mm: Move the slider to the 10-mm setting.
8 mm: Move the slider to the 8-mm setting.

Reference:

Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Current Medical Research & Opinion (2010; 26(6): 1519-1530).

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/s/

LAWRENCE D RODICHOK
08/25/2015

JOHN R MARLER
09/17/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

CHEMISTRY REVIEW(S)

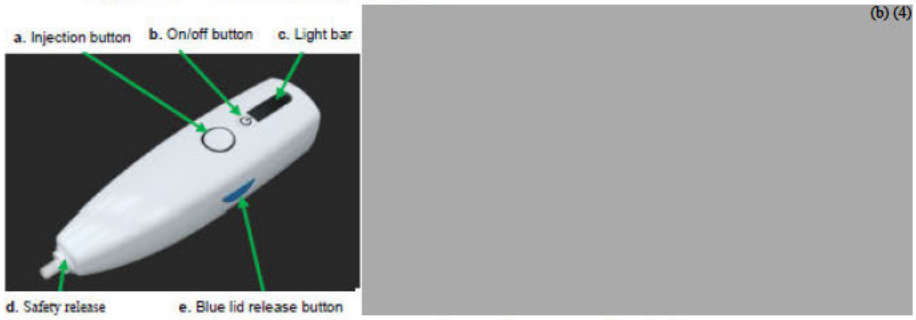
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

MEMORANDUM
To: File, BLA 103471/5186, CDER/ONP.
From: Ralph M. Bernstein, DBRB-IV.
Through: Cris Ausin, Team Leader DBRB-IV
Date: 21 August 2015
Submission Date: 25 Nov 2014
Action Date: 25 Sep 2015
Product: IFN-b, Betaseron® 103471-5186 (serial 0136).
License holder: Bayer HealthCare, PO Box 1000, Montville NJ 07045.
Manufacturer affected: Betaconnect Autoinjector: (b) (4) Medicom a/s (b) (4) Denmark (b) (4)
Product/Presentation: Lyophilized powder containing 0.3mg of IFNß-1b, 15 mg Human Serum Albumin (HSA), and 15 mg Mannitol, USP. A 0.54 % NaCl-solution PFS diluent is provided (one PFS per vial of DP).
Re: PAS for the use of a new autoinjector, the Betaconnect Autoinjector (b) (4) with a prepared Betaseron syringe.

Recommendation:
There are no CMC issues associated with this supplement. We (DBRB-IV) recommend approval of this supplement.

Background:
Betaseron is supplied as a lyophilizate (see "Product/Presentation" above) that requires reconstitution with 0.54% NaCl diluent from a diluent pre-filled syringe (PFS), resuspension, and withdraw of the solution from the vial into the diluent PFS. This is then injected from the PFS into the patient. In this PAS, the Sponsor, Bayer, proposes to allow patients the optional use of an electric assisted auto injector; namely, the Betaconnect autoinjector, (b) (4) Medicom (see Figure one, below).

Figure 1-1. BETACONNECT™ Features



The Betaseron syringe is prepared as for a regular injection and is immediately inserted into the Betaconnect autoinjector (b) (4). There is no change to the product-contacting container closure and no effect on CMC or product quality.

Reviewer comment:

Because there is no change in product-contacting container closure, and therefore no effect on product quality, we recommend approval of this supplement.

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/s/

RALPH M BERNSTEIN
08/21/2015

CRISTINA AUSIN-MORENO
08/21/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 25, 2015
Requesting Office or Division:	Division of Neurology Products
Application Type and Number:	BLA 103471/S-5186
Product Name and Strength:	Betaconnect Autoinjector for use with Betaseron (Interferon beta-1b) for Injection
Submission Date:	September 24, 2015
Applicant/Sponsor Name:	Bayer
OSE RCM #:	2014-2537-1
DMEPA Primary Reviewer:	Justine Harris, RPh
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

The Division of Neurology Products requested that we review the revised Betaseron Prescribing Information (PI), Betaconnect Instructions for Use (IFU), Betaconnect Quick Guide and Betaconnect carton labeling (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[1]

2 CONCLUSION

[1] Harris, J. Human Factors, Label and Labeling Review for Betaconnect for use with Betaseron (BLA 103471/S-5186). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 AUG 31. 23 p. OSE RCM No.: 2014-2537.

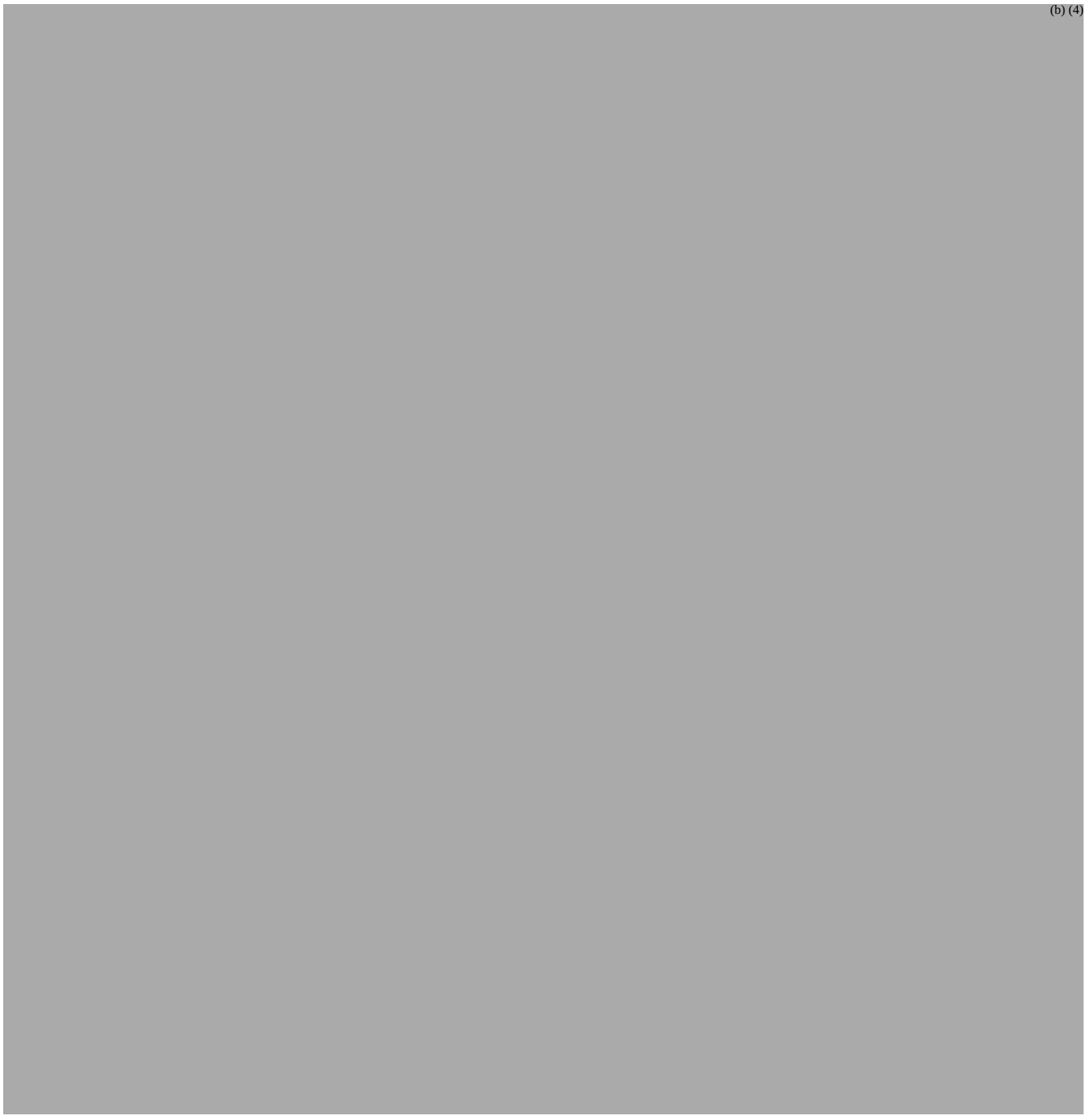
The revised Betaseron Prescribing Information (PI), Betaconnect Instructions for Use (IFU), Betaconnect Quick Guide and Betaconnect carton labeling, are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. LABEL AND LABELING SUBMITTED ON SEPTEMBER 24, 2015

- Betaseron Prescribing Information (no image)
- Betaconnect Carton Labeling
- Betaconnect Quick Guide
- Betaconnect IFU (no image)

Betaconnect Carton Labeling (portion of labeling showing revisions) :

(b) (4)

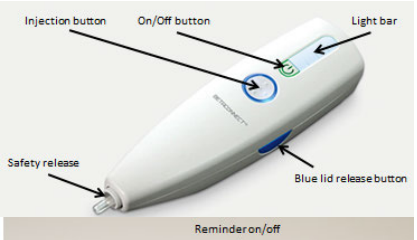


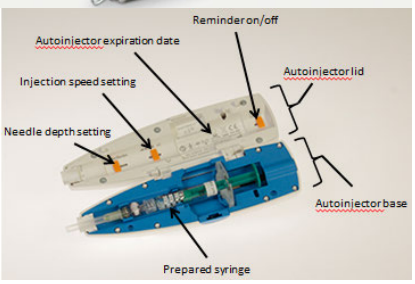
Betaconnect Quick Guide:

BETACONNECT™ autoinjector Quick Guide

Overview

Information: Use only a prepared BETASERON® syringe with attached capped needle.





Injection Process

The injection procedure is quiet. Do not remove BETACONNECT from the injection site until the device has shown that the injection is complete.

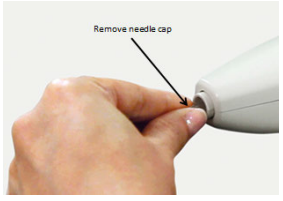
Step 1:
Press the **on/off button** to turn on the BETACONNECT.

Step 2:
Push the blue lid release button to open the lid.

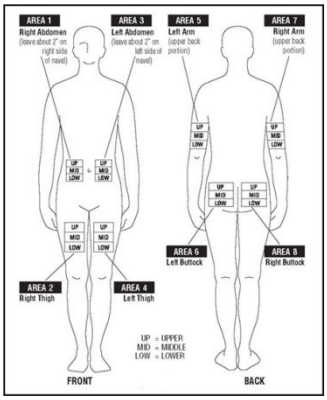
Step 3:
Place the syringe in the BETACONNECT base until it snaps into place.

Step 4:
Close the lid.

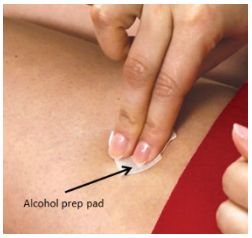
Step 5:
Remove needle cap.



Step 6:
Choose an injection site such as the stomach (abdomen), upper arm, thigh, or buttock. Change the injection site each time you give your injection.



Step 7:
Clean the injection site with an alcohol prep pad using a circular motion starting from the injection site and moving outward. Let the skin dry.



Step 8.
Place the BETACONNECT Autoinjector against the skin at a 90° angle (straight up and down).

Step 9:
Press the injection button to start the injection.

Step 10:
The lit blue bar will go down in stages as the injection progresses. Injection is complete when you hear short beeps and the light bar flashes blue.

Only remove the BETACONNECT from the injection site once the BETACONNECT has indicated that the injection is complete. Four blue reducing illuminated lights show the injection status. Injection is complete when you hear short beeps and the light bar flashes blue.

Version: 09/15

Manufactured by

Medicom Innovation Partner a/s
Gimsinglundvej 20
DK-7600 Struer
Denmark

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/s/

JUSTINE HARRIS
09/25/2015

DANIELLE M HARRIS
09/25/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 11, 2015

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Hamet Touré, PharmD, MPH
Regulatory Project Manager, DNP

From: Aline Moukhtara, RN, MPH, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD, Team Leader, OPDP

Subject: OPDP comments on the draft Prescribing Information (PI) for Betaseron (interferon beta-1b) injection

BLA: 103471, S-5186

On December 15, 2014, DNP consulted OPDP to review the draft Prescribing Information (PI), Medication Guide, Instructions for Use (IFU), and Quick Start for Betaseron (interferon beta-1b) injection (Betaseron), pertaining to a Prior Approval Supplement (PAS) 5186 submitted by the Sponsor for labeling revision to reference the optional use of the BETACONNECT Autoinjector.

OPDP reviewed the draft substantially complete version of the PI provided by DNP (Hamet Touré) on September 8, 2015. OPDP's comments on the draft PI are provided below.

A combined OPDP and DMPP review was conducted and comments on the draft Medication Guide, IFU, and Quick Start were sent under separate cover by DMPP on September 11, 2015.

If you have any questions, please contact Aline Moukhtara (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov.

17 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ALINE M MOUKHTARA
09/11/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 11, 2015
To:	Billy Dunn, MD, Director **Division of Neurology Products** **(DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Britt Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)** Mathilda Fienkeng, PharmD, Team Leader **Office of Prescription Drug Promotion (OPDP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Aline M. Moukhtara, RN, MPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG), Instructions for Use (IFU), and Quick Guide
Drug Name (established name):	BETASERON (interferon beta-1b)
Dosage Form and Route:	Solution for Subcutaneous Injection
Application Type/Number:	BLA 103471
Supplement Number:	S-5186
Applicant:	Bayer HealthCare Pharmaceuticals Inc.

1 INTRODUCTION

On November 25, 2014, Bayer HealthCare Pharmaceuticals submitted, for the Agency's review, a Prior Approval Supplement (PAS) for the approval of BETACONNECT Autoinjector for use with the prepared BETASERON syringe. BETASERON (interferon beta-1b) for subcutaneous use was originally approved on July 23, 1993 and is indicated for the treatment of relapsing forms of multiple sclerosis to reduce frequency of clinical exacerbations.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on December 15, 2014, and December 15, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed BETASERON (interferon beta-1b) Medication Guide (MG), BETACONNECT Autoinjector Instructions for Use (IFU), and BETACONNECT Autoinjector Quick Guide.

2 MATERIAL REVIEWED

- Draft BETASERON (interferon beta-1b) MG received on November 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 2, 2015.
- Draft BETASERON (interferon beta-1b) MG received on November 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 8, 2015.
- Draft BETACONNECT Autoinjector IFU and Quick Guide received on November 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 2, 2015.
- Draft BETACONNECT Autoinjector IFU and Quick Guide received November 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 8, 2015.
- Draft BETASERON (interferon beta-1b) solution for subcutaneous injection Prescribing Information (PI) received on November 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on September 2, 2015.
- Draft BETASERON (interferon beta-1b) solution for subcutaneous injection Prescribing Information (PI) received on November 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on September 8, 2015.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG, IFU, and Quick Guide documents using the Arial font, size 10.

In our review of the MG, IFU, and Quick Guide we have:

- simplified wording and clarified concepts where possible
- ensured that the MG, IFU, and Quick Guide are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG, IFU, and Quick Guide are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG, IFU, and Quick Guide meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG, IFU, and Quick Guide are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the MG, IFU, and Quick Guide are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG, IFU, and Quick Guide.

Please let us know if you have any questions.

54 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHARON W WILLIAMS
09/11/2015

ALINE M MOUKHTARA
09/11/2015

MARCIA B WILLIAMS
09/11/2015

HUMAN FACTORS, LABELS, AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	August 31, 2015
Requesting Office or Division:	Division of Neurology Products
Application Type and Number:	BLA 103471/S-5186
Product Name and Strength:	Betaconnect Autoinjector for use with Betaseron (Interferon beta-1b) for Injection
Product Type:	Combination Drug -Device
Rx or OTC:	Rx
Applicant/Sponsor Name:	Bayer
Submission Date:	November 25, 2014
OSE RCM #:	2014-2537
DMEPA Primary Reviewer:	Justine Harris, RPh
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS
Human Factors Specialist:	QuynhNhu Nguyen, MS
DMEPA Associate Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

Bayer has submitted a prior approval labeling supplement (PAS; S-5186) for modification to the Prescribing Information (PI) and Instructions for Use (IFU) for Betaseron. The change includes the listing of an optional, alternative delivery system to inject Betaseron utilizing the reusable electronic autoinjector called Betaconnect. The Betaconnect autoinjector has not previously been cleared by CDRH and is only being submitted as a combination product under the BLA. Thus, the Division of Neurology Products (DNP) consulted the Division of Medication Error Prevention and Analysis (DMEPA) to review the submitted Human Factors validation study report, labels, and labeling for Betaseron and the Betaconnect autoinjector submitted under the prior approval supplement.

Because the Betaconnect autoinjector will be distributed separately from Betaseron, Bayer proposes to modify the Betaseron dosage and administration section of the Prescribing Information (PI), and the instructions for use (IFU), to reference the optional use of the Betaconnect Auto Injector (BAI) for administration. There are no changes to the container closure system and the packaging for the currently marketed Betaseron packaging presentation.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Betaseron is currently approved as a single use vial which is administered by patients after mixing its contents with a syringe that is pre-filled with diluent (see Table 2, Relevant Product Information for Betaseron). With the proposed Betaconnect Auto Injector (BAI), the injection can be performed by the autoinjector once the user inserts the prepared Betaseron syringe into the autoinjector and completes the subsequent tasks involved in injecting the product. It should be noted that the autoinjector is designed with (b) (4) software (b) (4) for patients to (b) (4), and to (b) (4); however, (b) (4) are non-functional at this time and are not considered part of the approval package for this PAS; therefore, (b) (4) not the subject of this review.

Human Factors Summative Study Assessment

We evaluated the Human Factor Study Results for the two summative studies submitted on November 25, 2014. The design of the studies was identical except that in Study 1, the participants were trained by a healthcare provider (HCP) and were asked to return in one hour to perform their observed, simulated injection. In study 2, the users were provided the device without training and immediately performed their observed, simulated injection. Within the two studies, Bayer reported five failed injections, four of which occurred with the untrained user group when the users removed the Betaconnect from the injection site before the injection was complete (two in the first use trial, and two in the second use trial). The fifth failed injection occurred when the patient did not press the injection button to start the injection process. In addition, 4 participants (1 trained caregiver in Study 1, 3 untrained caregivers in Study 2) did not correctly respond to the questions in knowledge-based assessment regarding interpreting battery status and cleaning the device. The trained caregiver attributed the cause of the incorrect response to misinterpreting battery status due to wrong recollection from what they learned from training, and the three untrained caregivers reported that they responded based on their working assumptions and not because of product design.

Bayer believes that the failures associated with premature removal of the autoinjector from the injection site have been adequately addressed in IFU, where it specifies that (1) there are auditory and visual signals that serve as indicator to the user that the injection has been complete, and (2) the user should hold the autoinjector for the entire injection process. Thus, Bayer has determined that no further design changes are necessary to address the failures. Bayer's explanation is reasonable; if the user is not trained does not read the IFU before use, they may not be aware of the critical information to operate the autoinjector safely and effectively. Adding a statement recommending training before first use and reading the IFU may help to further reduce the risk for

failing to hold the autoinjector in place for the full time needed for injection. Additionally, clarity can be improved with regards to how to complete an injection if there is premature removal of the autoinjector from the injection site and the injection is interrupted, which we provide recommendations for below.

We note that the HF study did not assess injection site selection, however, instruction regarding this task is adequately provided in the approved Betaseron IFU, and we have no concerns that the optional addition of the BAI for injection would impact user performance for this aspect of the injection. In addition, we have not identified any post-marketing issues indicating that the instructions for injection site selection in the Betaseron IFU have led to use problems.

We note that the HF study does not assess the users' ability to perform adjustments to the injection speed and injection depth settings. We requested Bayer to provide a rationale as to why these functions were not tested. We accepted Bayer's rationale that they are optional settings primarily designed for patient's comfort. We also noted that the IFU contains statements instructing patients to first check with the MS nurse or healthcare provider prior to changing these settings. The medical officer recommends additions to the Betaseron PI Dosage and Administration Section that aligns with other approved injections for use in multiple sclerosis such as Rebif. The Rebif PI states the injection depth setting of the autoinjector and notes that the healthcare provider should determine injection technique for the patient. We concur and have included the medical officer's recommendations in Sections 4.1 and 4.2 below. We have determined that these changes will not require another HF validation study.

We also note that the HF study did not assess the users' ability to perform the optional setting of the reminder function. Bayer clarified that this is an optional tool reminding the user that 48 hours have passed since the last use of the autoinjector. We accepted Bayer's response and do not believe that this function is integral to successful dosing given that the currently marketed Betaseron does not offer this reminder option and the Instructions For Use specify "Use the built-in reminder only as a backup. It is still your responsibility to take Betaseron on schedule, every other day, and to follow the instructions from your healthcare provider."

To further inform our review, on May 15, 2015, we requested that Bayer provide differences between the internationally marketed device and the proposed US device and a summary of all complaints and errors seen with the existing internationally marketed device along with a root cause assessment for each. On May 29, 2015, Bayer confirmed that the Betaconnect autoinjector available in international markets is (b) (4). In

addition, they provided a summary of complaints for the internationally marketed product with root cause analysis, clinical impact and implemented corrective action for each. Based on Bayer's analysis of the internationally marketed device, we have not identified any additional concerns.

Labels and Labeling Assessment

Betaseron Labeling (PI, and IFU)

DMEPA reviewed the language Bayer proposes to include in the dosage and administration section of the Betaseron PI and in the IFU citing the optional use of the Betaconnect autoinjector for administration (see Appendix G.1.1) and have made recommendations for revisions to promote the safe and correct use of the product.

Betaconnect Labeling (IFU, Quick Guide, carton labeling, and device label)

In addition, we reviewed the IFU, Quick Guide and carton labeling and device label for the proposed Betaconnect autoinjector to determine whether there are any changes necessary to mitigate confusion that could result in medication errors. Our review of the proposed labels and labeling identified areas that can be improved to increase the readability and prominence of important information, to promote the safe and correct use of the product, to mitigate any confusion, and to clarify information. Specifically, we note that the [redacted] (b) (4) contained within the Betaseron IFU [redacted] (b) (4). This is important information pertaining to the [redacted] (b) (4) that should be included in the Betaconnect labeling. However, given that the tasks for choosing and preparing the [redacted] (b) (4) with Betaseron [redacted] (b) (4), we do not believe these changes to the user interface require additional human factors validation studies.

4 CONCLUSION & RECOMMENDATIONS

The human factors validation study identified failures of removing the autoinjector from the injection site prematurely. This can result in underdose and accidental exposure of drug to others. However, we note these failures primarily occurred with untrained participants. Though not powered to identify a difference, performance in the trained participants in the HF validation study suggests that the training may positively impact use of the product. Therefore, we recommend that Bayer includes a statement on Betaconnect carton labeling as well as the Betaconnect IFU that instructs the user that they should be trained on the use of the Betaconnect autoinjector by their healthcare provider before using the Betaconnect Autoinjector.

Bayer proposes to include, in the dosage and administration section of the Betaseron PI and in the IFU, information citing the optional use of the Betaconnect for administration. We recommend additional statements and revisions to promote the safe and correct use of the product. In addition, our review of the labels and labeling for the Betaconnect autoinjector identified areas that can be improved to promote safe and effective use of this product. We provide recommendations in Section 4.1 for the Division and recommendations to Bayer in Section 4.2 and advise they are implemented prior to approval of the supplement. We will not require another human factors validation study due to these requested changes.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. The proprietary name Betaconnect has been found to be conditionally acceptable. Therefore, add the name Betaconnect throughout the labels and labeling where appropriate instead of only noting the general term Autoinjector.

2. In Section 2.3 Important Administration Instructions, revise part (a) to include information about injection depth and proper injection technique as follows:

(b) (4)

4.2 RECOMMENDATIONS FOR BAYER

We recommend the following be implemented prior to approval of this BLA supplement. We will not require another human factors validation study due to these requested changes.

Betaseron Instructions for Use

A. In your proposed revision to IFU Step 5: Injecting BETASERON, include the statement ,

(b) (4)

Betaconnect Device Labels and Labeling

A. Betaconnect Autoinjector

1. We note that there are many symbols used on the Betaconnect Autoinjector and the meaning of these symbols is included in the IFU, Chapter 6 Technical Specifications. However, (b) (4) .

B. Betaconnect Instructions for Use and Quick Guide

1. Include in the (b) (4) of the IFU, a statement that patients should be trained on the use of Betaconnect Autoinjector prior to first use and should perform the first Betaseron injection using Betaconnect under the supervision of an appropriately qualified health professional to ensure that the device can be used safely and correctly by end users.

2. We note that the proposed IFU and Quick Guide (b) (4) . To increase clarity, we recommend that instruction regarding all injection sites be included in section 3.2, Injection (b) (4), of the IFU and Step 6 of the Quick Guide by adding an illustration and/or list of all recommended injection sites similar to what exists for Betaseron. Include full instructions for skin preparation prior to injection.

3. We determined that clarity can be improved with regards to how to complete an injection if there is premature removal of the autoinjector from the injection site and the injection is interrupted. We note that the IFU has information in Chapter 5, Troubleshooting, that the autoinjector will show a red blinking light if the injection procedure is interrupted or if a malfunction was detected with instructions on how to handle this problem, however, this information may be missed and should be included in Step 5, (b) (4), of the IFU.

4. Immediately prior to the injection instructions, include a list and/or figure of all additional supplies required for using the autoinjector, such as, prepared Betaseron syringe, alcohol pads, gauze, adhesive bandage, puncture-resistant sealable container, etc.

5. Revise the cautionary statement in Step (b) (4) of the Quick Guide to read, "Only remove the Betaconnect from the injection site once the Betaconnect has indicated that the injection is complete. Four blue reducing illuminated lights show the injection status. Injection is complete when you hear short beeps and the light bar flashes blue." This may help prevent interruption

of injection resulting in partial or missed doses. We recommend bolding the statement for increased prominence.

C. **Betaconnect Carton Labeling**

1. The [redacted] (b) (4). Include the net quantity statement by providing the total number of devices to read such as follows, "This carton contains one reusable autoinjector."

2. Include the specific purpose of product use, i.e. use with Betaseron only.

3. Include information on how to resource the BetaPlus program, such as, "If you have questions about your Betaconnect Autoinjector, talk with your BETA Nurse or healthcare provider, or call BETAPLUS at 1-800-788-1467 anytime."

4. Include a cautionary statement "For Single Patient Use Only" prominently placed below the proprietary name so that this important information is clearly visible and to reduce the likelihood of it being overlooked.

5. We note that the device has the expiration date printed on the inside cover, however, this important information should also be Included on the carton labeling to avoid being missed.

6. Include statements that instruct the user to read the IFU before first use for critical information regarding safe and correct operation of the autoinjector.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Betaseron that was approved January 28, 2014. The proposed autoinjector, Betaconnect, is proposed as an alternative to manual injection of BETASERON and therefore, the proposed PI will include a statement for this delivery option.

Table 2. Relevant Product Information for Betaseron	
Initial Approval Date	July 23, 1993
Active Ingredient	Interferon beta-1b
Indication	Relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations
Route of Administration	subcutaneous
Dosage Form	For Injection
Strength	0.3 mg
Dose and Frequency	Initial dose is 0.0625 mg (0.25 mL) subcutaneously every other day, with dose increases over a 6 week period to the recommended target dose of 0.25 mg every other day
How Supplied	Product is supplied as a lyophilized powder in a clear glass, single use vial (3 mL capacity). Each vial is contained within its own separate (single use) carton and there are 14 of these cartons contained within a larger carton. Each single use carton contains: • vial of Betaseron • Pre-filled single use syringe containing 1.2 mL diluent (Sodium Chloride, 0.54 % solution) • A vial adapter with a 30-gauge needle attached • 2 alcohol prep pads
Storage	Store Betaseron vials at room temperature 68°F to 77°F (20°C to 25°C). Excursions of 59°F to 86°F (15°C to 30°C) are permitted for up to three months. After reconstitution, if not used immediately, refrigerate the reconstituted solution and use within three hours. Do not freeze.

Container Closure	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched the L: drive on June 23, 2015 using the terms, Betaseron and Betaconnect, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous label and labeling reviews, which evaluated the PI, MG, and IFU for Betaseron and two reviews for Betaconnect[1][2][3][4][5]. We evaluated these reviews to help inform our current review and determined that all of our previous recommendations had been implemented.

[1] White, L. Proprietary Name Review for Betaconnect Autoinjector for use with Betaseron (Interferon beta-1b) for Injection (BLA 103471/S-5186) Silver Spring (MD): FDA, CDER, OSE, DMEPA(US); 2015 APR 6. Panorama #: 2015- 189541.

[2] Baugh D. Response to Questions in Pre-sBLA Meeting Package for Betaconnect AutoInjector for use with Betaseron for Injection (BLA 103471) Silver Spring (MD): FDA, CDER, OSE, DMEPA(US); 2014 SEP 22. 8 p. OSE RCM No.: 2014-1420.

[3] Neshiewat J. Labeling Memorandum for Betaseron (Interferon Beta-1B) Injection 0.3 mg (BLA 103471/S-5185) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 NOV 18. 13 p. 2 OSE RCM No.: 2013-2370.

[4] Neshiewat J. Label, Labeling, and Packaging Review for Betaseron (Interferon Beta-1B) Injection 0.3 mg (BLA 103471/S-5180) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 SEP 05. p 8. OSE RCM No.: 2013-757.

[5] Neshiewat J. Label, Labeling, and Packaging Review for Betaseron (Interferon Beta-1B) Injection 0.3 mg (BLA 103471/S-5125) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 APR 19. p 19. OSE RCM No.: 2013-44.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

We evaluated the Human Factor Study Results for the two summative studies submitted on November 25, 2014[6]. Below is a brief overview of the study objectives, descriptions of study participants, study design, data collection, and data analysis.

> The design of the studies was identical except that in Study 1, the participants were trained by a healthcare provider (HCP) and were asked to return in one hour to perform their observed, simulated injection. In study 2, the users were provided the device without training and immediately performed their observed, simulated injection. Participants used an injection pad placed on their body wherever they would normally inject. Caregivers were provided with a manikin and were asked to place the injection pad on the manikin wherever they normally inject their patient. During the simulation, the moderator observed the participants' ability to complete each use step. If participants said at any time, they would contact a Beta Nurse or doctor, they were provided with a phone they could use to call a Beta Nurse, and the nurse would provide assistance. Once participants finished the injection, the moderator collected ratings data to assess participants' confidence that they had performed the injection correctly and the ease of performing the injection. The moderator then probed for root cause for any close calls or failures. Participants were then asked to interpret the device's battery status, demonstrate the proper charging procedure, and show or describe how they would clean the device. Finally, participants who stated they used multiple sites to inject were asked to demonstrate a simulated injection on one alternative injection site using an air-filled syringe without a needle to ensure that participants could safely and effectively administer the injection using any sites they regularly use.

Study Objective: To validate that the Betaconnect can be used by its intended users without patterns of preventable use errors that would cause user or patient harm. To the extent that use errors may occur, this study was designed to collect sufficient and appropriate data such that these failures could be explained in terms of their cause from the perspective of the representative users so that they can be fully understood and if appropriate, further controlled.

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[6] On September 22, 2014, DMEPA participated in a pre-sBLA meeting between Bayer and the Agency to discuss Bayer's intent to market proposed auto-injector for administration of Betaseron. In the pre-meeting package, DMEPA responded to the question related to Human Factors and Design Validation and concluded that we had insufficient information about how the study was conducted to determine whether it is adequate to validate the use of the Betaconnect. We communicated that we would be unable to provide agreement that the studies are adequate to support the use of the BAI without a comprehensive review of the study results and associated use-related risk analysis. In addition, we provided minimum requirements for the study report that will be submitted.[6] On November 25, 2014 Bayer submitted the results of their human factors summative studies and the revised Prescribing Information (PI), and Instructions for Use (IFU) for Betaseron and the proposed IFU and Quick Guide for the Betaconnect Autoinjector (BAI).

Study Participants: Both summative studies were conducted consisting of 31 participants (16 MS patients, 15 caregivers of MS patients) in each. All patient participants were current Betaseron users who perform their own injections.

Training: The trained study participants (Study 1 only) received the type of instruction consistent with that, which would be expected for devices in commercial distribution. Training was provided by Beta Nurses and covered all steps of the injection process including frequently used functions such as interpreting battery status, charging the battery, and cleaning the device. Nurses introduced the device to participants, then using the device, the IFU and Quick Guide provided explanations and demonstrations of each step to the participant. Participants were encouraged and allowed to ask questions. Following the training, the participant was given a prepared syringe and asked to use the device to perform an injection into an injection pad, simulating the first use of the device in the HCP presence. Retraining was given to participants who had difficulty performing the injection and were given 3 opportunities to correctly and independently perform the injection. After the first successful injection attempt, participants were asked to demonstrate how they would use the device on alternative injection sites.

Tasks:

Task	Operation Step	Success Criteria	Task Priority
Injection Process	Step 1: Turn on the device on	Participant presses power button to elicit confirmation beeping.	Low Priority
	Step 2: Open device	Participant presses blue lid release button to open case lid.	Low Priority
	Step 3: Place the prepared syringe system into the insertion area	Participant takes prepared syringe and places it into insertion area until it snaps into place.	Low Priority
	Step 4: Close device	Participant closes the lid.	Low Priority
	Step 5: Remove needle cap	Participant removes the needle cap by pulling it off the front of the device. The participant does not get injured during the removal.	Low Priority

	Step 6: Hold the device against the intended injection site to activate the safety release	Participant holds the device and presses against the intended place for injection in a way where it is possible to activate the injection button.	Low Priority
	Step 7: Press injection button	Participant presses the injection button at least until the injection process has been started.	Low Priority
	Step 8: Injection and injection status	Participant hold the device against the injection site for the entire injection time.	High Priority
	Step 9: Remove from injection site	Participant removes the device from injection site after the completion of the injection is indicated by short beeps and a flashing blue light.	Low Priority
	Step 10: Open the lid	Participant presses blue lid release button to open case lid.	Low Priority
	Step 11: Remove syringe	Participant removes the syringe from the device.	Low Priority
Other Frequently Used Functions	Step 12: Determining device battery status	Participant can understand the battery status light bar.	Low Priority
	Step 13: Charging the battery	Participant can connect the device with charger.	Low Priority
	Step 14: Cleaning of the device	Participant can understand the cleaning instruction and can demonstrate in practice.[2]	Low Priority

The only task considered critical (high priority) was holding the Betaconnect to the injection site until the injection was completed (Step 8). The user tasks of selecting the injection speed and depth, and setting the reminder function were not assessed as Bayer states these functions are provided set in the default mode and resetting them is optional and not necessary to use and achieve a successful injection with the Betaconnect. Bayer also considered these functions not high priority tasks as a use error cannot cause any user harm or mis-dosing.

Definition of Performance Success/Failures:

The overall outcome was scored for each attempted injection by capturing performance data on the specific operation steps required to complete the injection. Each step of the injection process was evaluated in relation to the degree of fulfillment, and was scored according to the same definitions as the overall injection. Definitions are as follows:

- Success: After reading the labeling materials to complete the task, the participant accomplished the step/task, regardless of the duration it took to complete it.
- Success with guidance: If participants said at any time that they would contact a Beta Nurse or doctor, they were provided with a phone they could use to call a Beta Nurse who had performed the reconstitution screening. The Beta Nurse asked the participant to describe the difficulty they were experiencing, and the nurse would provide assistance.
- Close call: Any instance of a potential safety critical error that was avoided by vigilance on the part of the participant.
- Use Error: Participant did not complete a step/task in accordance with the intended use or the use resulted in a wrong result.

When close calls and use errors occurred, moderators would ask follow up questions after the participant's attempt on the task was completed.

C.2 Results

Study 1 (Trained Users) Results

All trained participants (16/16 patients, 15/15 caregivers) successfully administered a simulated injection during their first attempt. All but one (11/11 patients, 13/14 caregivers) successfully administered a simulated injection during the second attempt at an alternate site. There were no critical failures, though one participant did abandon using the autoinjector to complete an injection because she believed it had malfunctioned; in that event, the participant said she would perform the injection manually or use a different autoinjector. The use error was considered an injection failure because instead of calling for assistance, the user determined she would have given herself an injection manually. When the user was instructed to call the Nurse, the issue was resolved and she was able to perform the injection successfully.

Figure 8-1: Overall Injection Outcomes – Study 1 Trained Patients

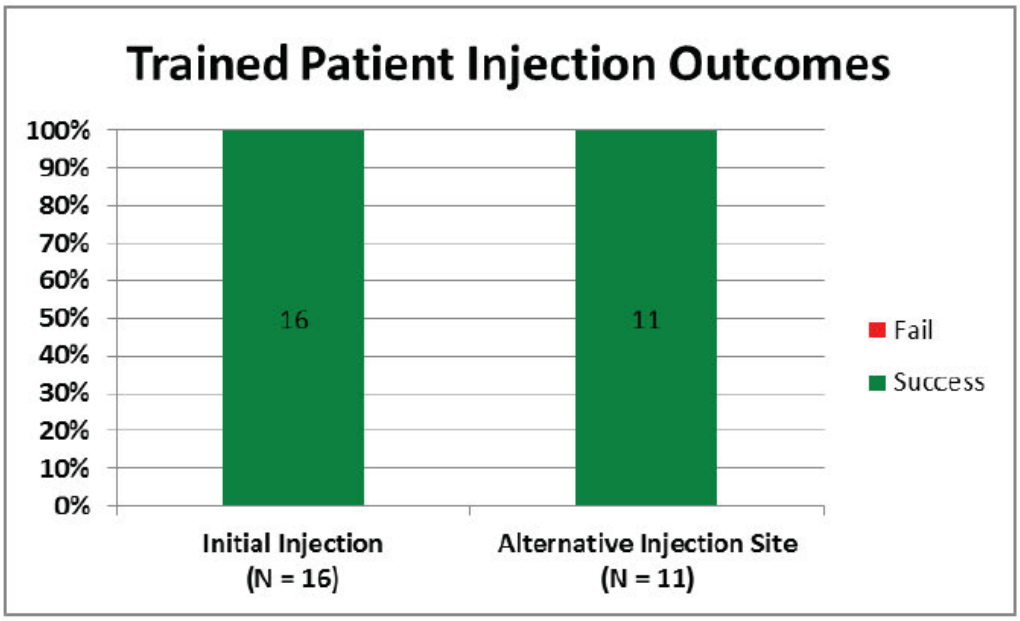


Figure 8-2: Overall Injection Outcomes – Study 1 Trained Caregivers

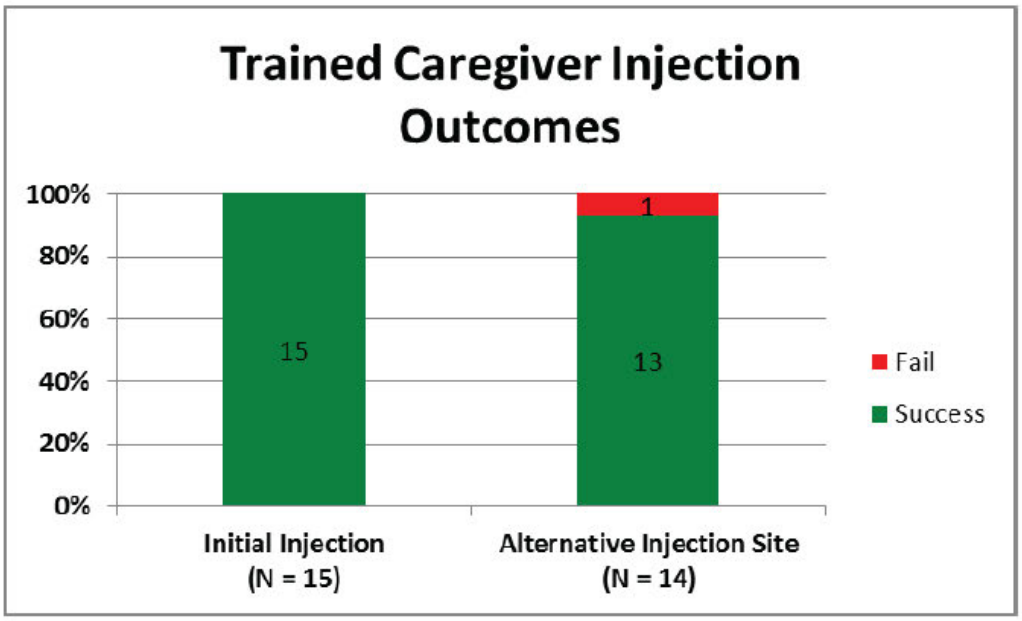


Table 8-5: Injection Sites Selected – Trained Participants – Study 1

	Patients		Caregivers	
	Initial Injection Site	Alternative Injection Site	Initial Injection Site	Alternative Injection Site
Thigh	13	1	8	0
Abdomen	3	5	5	2
Arm	0	2	2	6
Buttocks	0	3	0	6

Study results for the frequently used functions are as follows:

Interpret Battery Status	16/16 patients and 14/15 caregivers succeeded; one caregiver mistook 75% charged for fully charged. The participant stated that they had learned in the training that 3 squares on the light bar meant fully charged.
Charge the Battery	16/16 patients and 15/15 caregivers successfully connected the charger to the autoinjector
Clean the Device	4/16 patients and 5/15 caregivers referred to the cleaning instructions in the IFU, either independently or after being instructed to do so by the moderator; 16/16 patients and 15/15 caregivers successfully described or demonstrated the correct technique for cleaning the device, specifically wiping the low-force automatic safety release with alcohol or a damp cloth.

Study 2 (Untrained Users) Results:
Fifteen of 16 patients and 13 of 14 caregivers successfully administered a simulated injection during their first attempt. 8/9 patients and 7/9 caregivers successfully administered a simulated injection during the second attempt at an alternate injection site.

Figure 8-5: Overall Injection Outcomes – Study 2 Untrained Patients

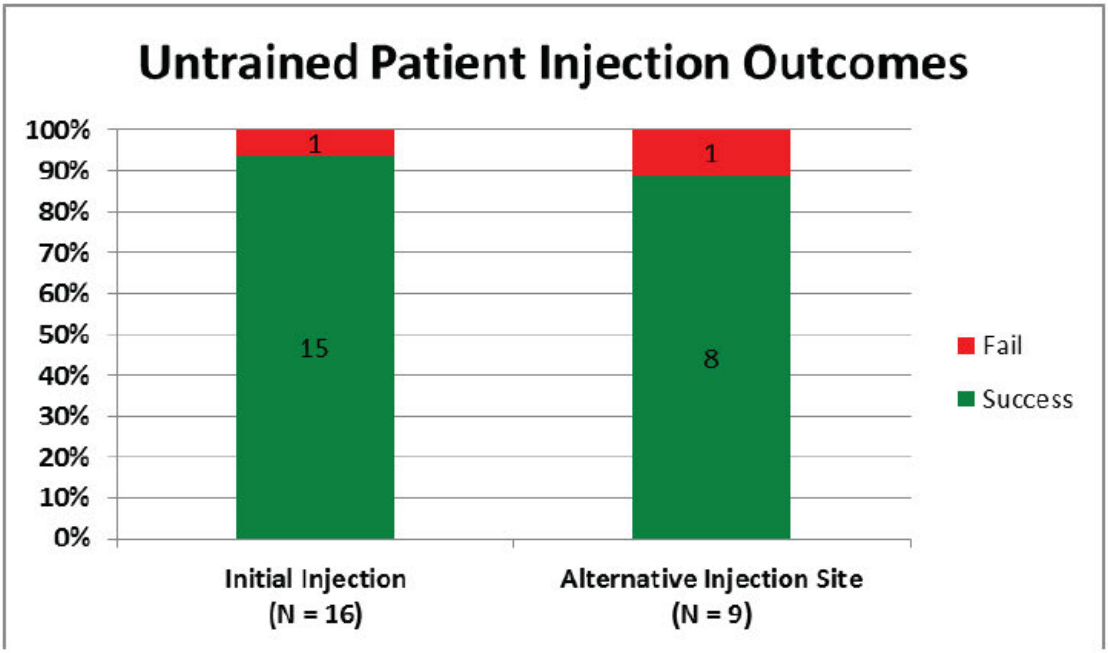
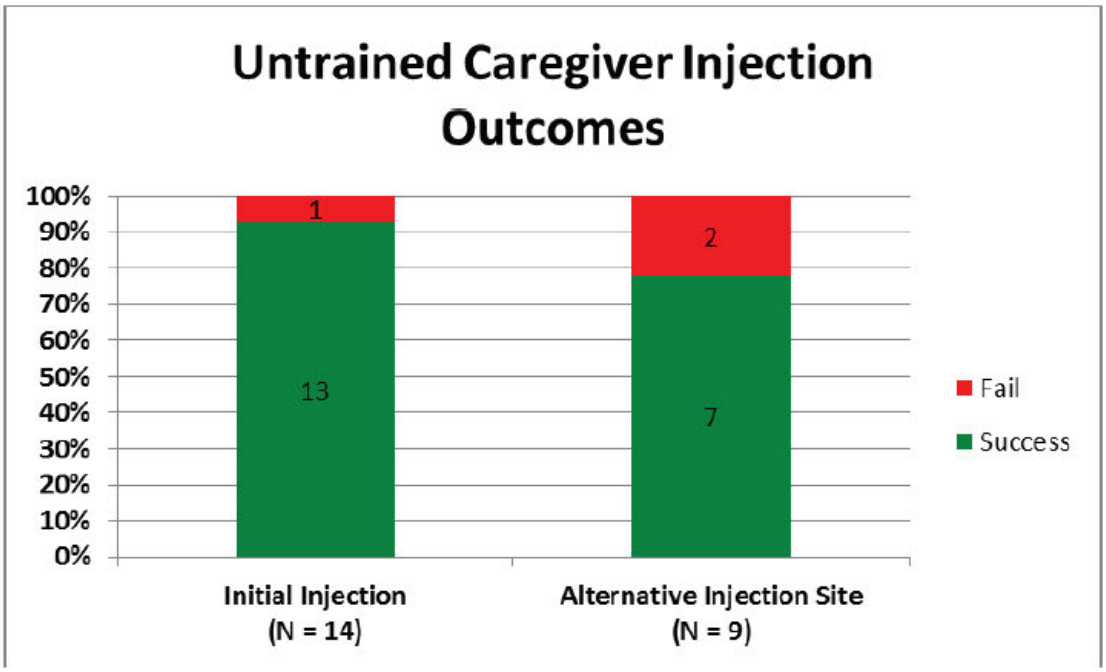


Figure 8-6: Overall Injection Outcomes – Study 2 Untrained Caregivers



Bayer stated that the isolated failures were due to the participants' existing mental models and their lack of familiarity with an electro-mechanical auto-injection device.

Study results for the frequently used functions are as follows:

Interpret Battery Status	16/16 patients and 14/15 caregivers succeeded; • All participants saw the battery status either as fully charged or 75% charged. • Nearly all participants successfully turned on the device and correctly interpreted the battery status. • One caregiver mistook 75% charged for fully charged. The participant stated that they believed the last square of the light bar would light up red if the device needed to be charged. This assumption was based on her expectations for how the device would function.
Charge the Battery	16/16 patients and 15/15 caregivers successfully connected the charger to the autoinjector
Clean the Device	6/16 patients and 13/15 caregivers referred to the cleaning instructions in the IFU, either independently or after being instructed to do so by the moderator; 16/16 patients and 13/15 caregivers successfully described or demonstrated the correct technique for cleaning the device, specifically wiping the low-force automatic safety release with alcohol or a damp cloth. 2/15 caregivers failed to correctly interpret the instructions for cleaning because they believed the blue lid release button was the low-force automatic safety release.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[7] along with postmarket medication error data, we reviewed the following:

- Betaseron Prescribing Information (PI) and IFU which were approved January 28, 2014, addition of proposed language for optional use of Betaconnect autoinjector (G 1.1)
- Betaconnect Printing on device (G 1.2)
- Betaconnect Printing on carrying case (G 1.3)
- Betaconnect Carton label (G 1.4)
- Betaconnect Quick Guide (G 1.5)
- Betaconnect IFU (no image)
- Betaconnect MG (no image)

G.1.1 Bayer's Proposed language for the Betaseron PI and IFU

PI Section 2.3 (b) (4)

(b) (4)

(b) (4)

IFU Step 5: Injecting BETASERON

Optional Use of (b) (4) You may (b) (4) . For more information, call BETAPLUS, the BETASERON patient support program, at 1-800-788-1467.

[7] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

G.1.2 Printing on device

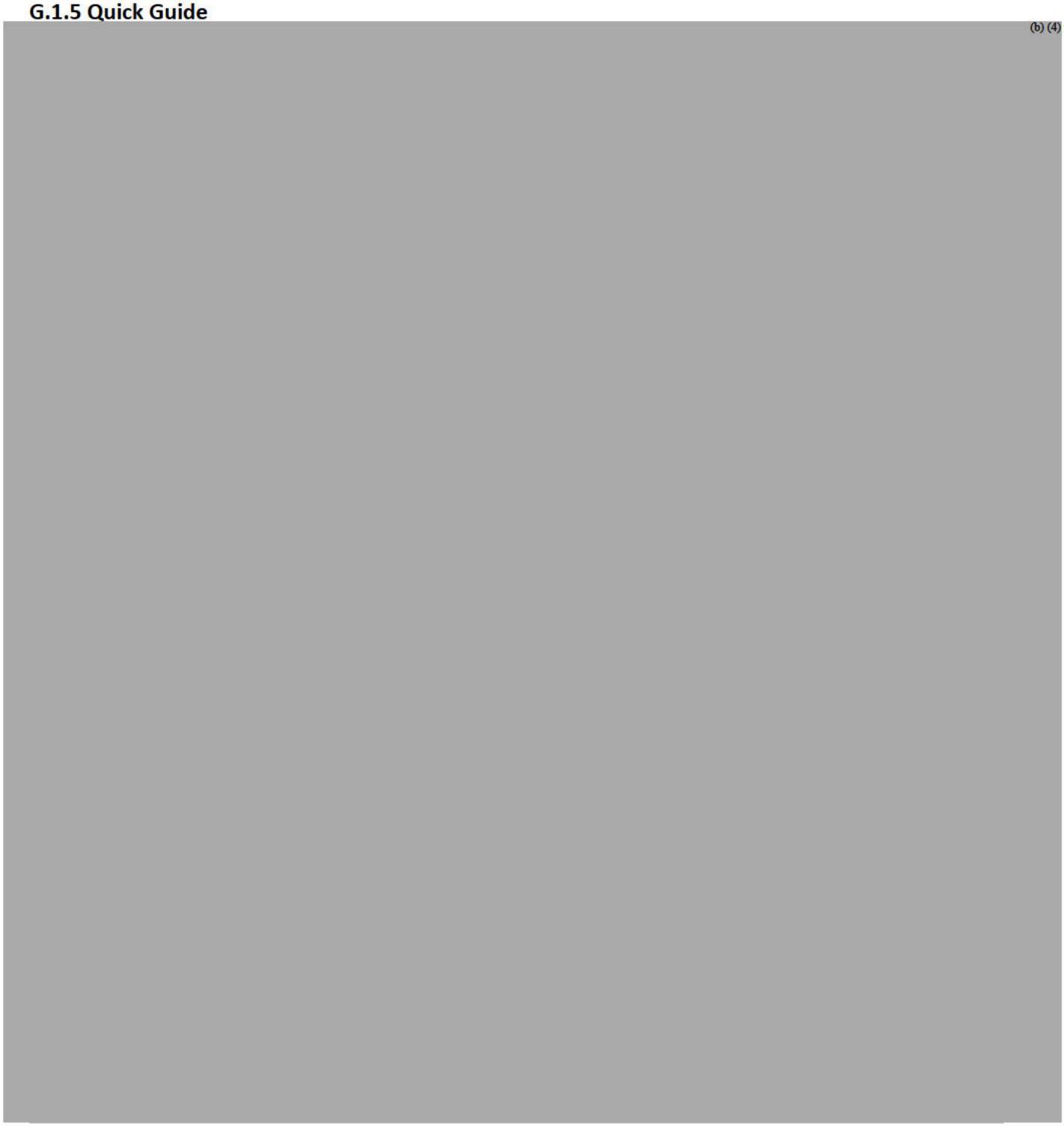
BETACONNECT exterior - bottom

Printing on BETACONNECT Autoinjector inside (top)

G 1.3 Printing on carrying case

G.1.4 Carton label

G.1.5 Quick Guide



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/s/

JUSTINE HARRIS
08/31/2015

DANIELLE M HARRIS
08/31/2015

IRENE Z CHAN
08/31/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 6, 2015
Application Type and Number:	BLA 103471/S-5186
Product Name and Strength:	Betaconnect Autoinjector for use with Betaseron (Interferon beta-1b) for Injection
Product Type:	Combo
Rx or OTC:	RX
Applicant/Sponsor Name:	Bayer
Submission Date:	April 16, 2015
Panorama #:	2015- 189541
DMEPA Primary Reviewer:	Lolita White, PharmD
DMEPA Team Leader:	Danielle Harris, PharmD, BCPS

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Betaconnect, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 PRODUCT INFORMATION

The following product information is provided in the April 16, 2015 proprietary name submission.

- Intended Pronunciation: [BAY-tuh-con-NECT]
- Active Ingredient: BETASERON® (interferon beta-1b) is an approved drug for the treatment of multiple sclerosis. The supplement BLA 103471/S-5186 is to request approval of an autoinjector for use with prepared BETASERON syringe.
- Indication of Use: Autoinjector for use with prepared BETASERON syringe.
- Route of Administration: Autoinjector will be used to administer subcutaneous BETASESRON injections
- Dosage Form: n/a
- Strength: n/a
- Dose and Frequency: n/a
- How Supplied: The autoinjector is a reusable device and will be distributed separately from BETASERON.
- Storage: n/a
- Container and Closure Systems: n/a

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division Neurology Products (DNP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[1].

2.2.2 Components of the Proposed Proprietary Name

This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

The Applicant indicated in their submission that the proposed name, Betaconnect, is for an Autoinjector to be used with the prepared BETASERON syringe. The "BETA" portion of the autoinjector name is derived from the BETASERON name, and the "BETA" prefix identifies that the autoinjector is intended use with BETASERON. .

The "CONNECT" portion of the name is to convey the sense of "connectedness" that the autoinjector may provide to patients for administering their BETASERON. The autoinjector has two main areas of interface with patients, these being (1) adjustable settings that patients can select (e.g. injection speed and depth); and (2) audio and/or visual communications that the autoinjector can provide to patients (e.g. battery charge indicator, ready-to-inject visual signal, progress indicator for the injection process, audio-visual end-of-dose signal and audio-visual injection reminder, etc.). The customizable settings and ability to communicate before, during and after the injection process combine for a "connection" between patient and his/her BETASERON treatment.

2.2.3 FDA Name Simulation Studies

77 practitioners participated in DMEPA's prescription studies. One response did overlap with the currently marketed product, Betaseron. The overlap is discussed in Section 2.2.6. None of the other responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, May 6, 2015 e-mail, the Division of Neurology Products (DNP) stated concerns with the proposed proprietary name, Betaconnect as it may be misinterpreted as having the ability to provide a connection to a mobile app since the product and app are marketed in Europe with videos and webpages with instructions on how to use the app with the Betaconnect device. However, the division deferred to DMEPA's review to determine any risk for medication error that can be attributed to the proposed proprietary name.

We considered DNP's concern, and we determined that if a person is familiar with the European device and questions why they are unable to connect to an application with the U.S. device, they will likely contact the Applicant for clarification. Although the autoinjector Betaconnect is already marketed and functions with blue tooth connectivity in Europe, we determined this device can be safely marketed under the proposed name.

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[1]USAN stem search conducted on 05/16/15

2.2.5 *Phonetic and Orthographic Computer Analysis (POCA) Search Results*

Table 1 lists the number of names with the combined orthographic and phonetic score of ≥50% retrieved from our POCA search[2] organized as highly similar, moderately similar or low similarity for further evaluation. Table 1 also includes names identified from the FDA Prescription Simulation.

Table 1. POCA Search Results	**Number of Names**
Highly similar name pair: combined match percentage score ≥70%	2
Moderately similar name pair: combined match percentage score ≥50% to ≤ 69%	262
Low similarity name pair: combined match percentage score ≤49%	0

2.2.6 *Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities*

Our analysis of the 264 names contained in Table 1 determined none pose a risk for confusion as described in Appendices C through H.

We note that one respondent interpreted the outpatient prescription as Betaseron. Betaseron is currently available on the market and is to be used with Betaconnect. The outpatient prescription was written as: Betaconnect, Use to inject Betaseron 0.25 mg every other day. Since Betaconnect is only designed to be used with Betaseron, this misinterpretation is unlikely to result in any meaningful safety concern or medication error.

2.2.7 *Communication of DMEPA's Analysis at Midpoint of Review*

DMEPA communicated our findings to the Division of Neurology Products (DNP) via e-mail on June 24, 2015. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DNP on June 30, 2015, they stated no additional concerns with the proposed proprietary name, Betaconnect.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Ermias Zerislassie, OSE project manager, at 301-796-0097.

[2] POCA search conducted on 05/16/15

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Betaconnect, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your April 16, 2015 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved brand name and generic drugs; therapeutic biological products, prescription and over-the-counter human drugs; and discontinued drugs (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent

Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNCE. OPDP or DNCE evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNCE provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3]

[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥50% to ≤ 69%.
- Low similarity: combined match percentage score ≤49%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair do not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥50% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: o Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. o Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. o Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤49%).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Betaconnect Study (Conducted on 5/8/15)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order: Betaconnect Use to inject betaseron 0.25 mg Subcutaneously every other day	Betaconnect Use as directed dispense #1
Outpatient Prescription: Betaconnect use as directed #1	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

246 People Received Study

77 People Responded

Study Name: Betaconnect			
Total	**25**	**26**	**26**

INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
BELACONNECT	0	0	5	5
BETA CONNECT	0	8	0	8
BETACONAECT	0	0	1	1
BETACONECT	0	1	1	2
BETACONNECT	17	12	16	45
BETA-CONNECT	0	1	0	1
BETACONNECT BETASERON	0	0	1	1
BETACONNECT/BETASERON	0	0	1	1
BETACONNET	0	1	0	1
BETACONREET	2	0	0	2
BETACONVECT	1	0	0	1
BETACONVEET	2	0	0	2
BETACONVEST	1	0	0	1
BETACORVECT	1	0	0	1
BETACORVIECT	1	0	0	1
BETAKINECT	0	1	0	1
BETAKINEKT	0	1	0	1
BETAPENECT	0	1	0	1
BETASERON	0	0	1	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name: betaconnect** **Strength(s): none/device** **Usual Dose: Autoinjector used with Betaseron to deliver 0.625 mg – 0.25 mg subcutaneously every other day**	**POCA Score (%)**	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion**
1.	betaconnect***	100	Proposed name under this review
2.	DEPAKOTE CP	72	Orthographic: The prefixes, infixes and suffix of this name pair have sufficient orthographic differences. Phonetic: When comparing Betaconnect to the root name, Depakote, the first syllables (bay vs dep) and third syllables (con vs kote) of this name pair sound different, and the proposed Betaconnect name contains an extra syllable. Depakote CP also contains the modifier "CP" helping the names sound different when spoken, if included.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Proposed Name	POCA Score (%)
1.	(b) (4)	50
2.	(b) (4)	50
3.	(b) (4)	50
4.	(b) (4)	50
5.	(b) (4)	50
6.	(b) (4)	50
7.	(b) (4)	50
8.	(b) (4)	50
9.	DYLOJect	50
10.	(b) (4)	50
11.	(b) (4)	50

12.	BENZONATATE	51
13.	(b) (4)	51
14.	(b) (4)	51
15.	MetaTENSIN	51
16.	NEO Tect KIT	51
17.	(b) (4)	51
18.	(b) (4)	52
19.	(b) (4)	52
20.	(b) (4)	52
21.	(b) (4)	52
22.	(b) (4)	52
23.	(b) (4)	52
24.	DUetacT	52
25.	(b) (4)	52
26.	(b) (4)	52
27.	BEconASE AQ	54
28.	betaPACE AF	54
29.	betOPTIC	54
30.	(b) (4)	54
31.	(b) (4)	54
32.	(b) (4)	54
33.	BEconASE	55
34.	betaPACE	55
35.	(b) (4)	55
36.	BECLOVENT	56
37.	(b) (4)	56
38.	betaPRONE	56
39.	DEXacoRT	56
40.	DIMetaNE-DX	56
41.	(b) (4)	56
42.	(b) (4)	58

43.	MetaDATE CD	58
44.	betaXON	60
45.	(b) (4)	60
46.	(b) (4)	62
47.	(b) (4)	62
48.	(b) (4)	62
49.	(b) (4)	64

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name: betaconnect** **Strength(s): none/device** **Usual Dose: Autoinjector used with Betaseron to deliver 0.625 mg – 0.25 mg subcutaneously every other day**	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	(b) (4) C	50	When comparing Betaconnect to the root name (b) (4), the infixes and suffixes of this name pair have sufficient orthographic differences. The second and third syllables of this name pair sound different, and the proposed Betaconnect name contains an extra syllable.
2.	(b) (4)	50	The infixes and suffixes of this name pair have sufficient orthographic differences. The second, third and fourth syllables of this name pair sound different.
3.	(b) (4)	50	When comparing Betaconnect to the root name (b) (4), the suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name Benzac, the second and second syllables of Betaconnect sound different and Betaconnect has two additional syllables.
4.	(b) (4)	50	The infixes and suffixes of this name pair have sufficient orthographic differences. The third syllable sounds different. Betaconnect has an extra syllable.
5.	(b) (4)	50	When comparing Betaconnect to the root name (b) (4), the infixes and suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name (b) (4), the third syllable sounds different. Betaconnect has an extra syllable.
6.	betHAnecHOL	50	The infixes and suffixes of this name pair have sufficient orthographic differences. The second, third and fourth syllables of this name pair

			sound different.
7.	BISacoDYL	50	The prefixes, infixes and suffixes of this name pair have sufficient orthographic differences. The first, third and fourth syllables of this name pair sound different.
8.	BUTAZONE	50	The infixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllable sounds different. Betaconnect has an extra syllable.
9.	BUTOconAZOLE	50	The infixes and suffixes of this name pair have sufficient orthographic differences. The first, and fourth syllable sound different. (b) (4) has an extra syllable.
10.	(b) (4)	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllable sound different. Betaconnect has an extra syllable.
11.	(b) (4)	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllable sound different. Betaconnect has an extra syllable.
12.	(b) (4)	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllable sound different. Betaconnect has an extra syllable.
13.	DEFLAZacoRT	50	The prefixes, infixes and suffixes of this name pair have sufficient orthographic differences. The first and last syllable sound different.
14.	(b) (4)	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first, second and third syllable sound different. Betaconnect has an extra syllable.
15.	(b) (4)	50	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
16.	(b) (4)	50	The prefixes and infixes of this name pair have sufficient orthographic differences.

			The first syllable sounds different. Betaconnect has two extra syllables.
17.	(b) (4)	50	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
18.	(b) (4)	50	When comparing Betaconnect to the root name (b) (4), the prefixes and infixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name (b) (4) the first and second syllables sound different Betaconnect has an extra syllable.
19.	(b) (4)	50	When comparing Betaconnect the root name (b) (4) the infixes and suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect the root name (b) (4) the the first and second syllables sound different and Betaconnect has two extra syllables.
20.	(b) (4)	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllable sounds different. The name Betaconnect has an extra syllable.
21.	TEXacoRT	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. The name Betaconnect has an extra syllable.
22.	(b) (4)	50	The prefixes and suffixes of this name pair have sufficient orthographic differences. The third syllable sounds different and the name Betaconnect has an extra syllable.
23.	beta-ALANINE	51	The infixes and suffixes of this name pair have sufficient orthographic differences. The third and fourth syllables sound different. Beta-alanine has an extra syllable.
24.	beta-ESCIN	51	The infixes and suffixes of this name pair have sufficient orthographic differences. The third and fourth syllables sound different.
25.	(b) (4)	51	The prefixes and infixes of this name pair have

			sufficient orthographic differences. The first, second and third syllables sound different.
26.	(b) (4)	51	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. Betaconnect has an extra syllable.
27.	(b) (4)	51	When comparing Betaconnect to the root name (b) (4), the prefixes and infixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name (b) (4), the first and third syllables sound different. Betaconnect has an extra syllable.
28.	betaLIN S	52	When comparing Betaconnect to the root name betalin, the suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name betalin, the third syllables sound different. Betaconnect has an extra syllable.
29.	(b) (4)	52	The infixes and suffixes of this name pair have sufficient orthographic differences. The second and third syllables sound different. Betaconnect has an extra syllable.
30.	BOTOX COSMETIC	52	The prefixes, infixes and suffixes of this name pair have sufficient orthographic differences. The first, second and third syllables sound different.
31.	BUDESONIDE	52	The prefixes, infixes and suffixes of this name pair have sufficient orthographic differences. The first, third and fourth syllables sound different.
32.	(b) (4)	52	The infixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllables sound different.
33.	CEFetaMET	52	The prefixes and infixes of this name pair have sufficient orthographic differences. The first, second and third syllables sound different.
34.	DERMacoRT	52	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. Betaconnect has an extra syllable.

35.	(b) (4)	52	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and fourth syllables sound different.
36.	(b) (4)	52	When comparing Betaconnect to the root name Predacort, the prefixes and suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name Predacort, the first and third syllables sound different. Betaconnect has an extra syllable
37.	(b) (4)	52	The prefixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
38.	(b) (4)	52	The infixes of this name pair have sufficient orthographic differences. The third syllable sounds different. Betaconnect has an extra syllable.
39.	(b) (4)	52	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and last syllables sound different. Betaconnect has an extra syllable.
40.	(b) (4)	52	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first syllables sound different. Betaconnect has an extra syllable.
41.	BIMATOPROST	53	The infixes and suffixes of this name pair have sufficient orthographic differences. The third and fourth syllables sound different.
42.	(b) (4)	53	The prefixes and infixes of this name pair have sufficient orthographic differences. The first, second and third syllables sound different.
43.	BACIGUENT	54	The infixes and suffixes of this name pair have sufficient orthographic differences. The second, third and fourth syllables sound different.
44.	(b) (4)	54	The infixes of this name pair have sufficient orthographic differences. The first syllable sounds different. Betaconnect has an

			extra syllable
45.	beta MED	54	The suffixes of this name pair have sufficient orthographic differences. The third syllable sounds different. Betaconnect has an extra syllable.
46.	betaGAN	54	The suffixes of this name pair have sufficient orthographic differences. The third syllable sounds different. Betaconnect has an extra syllable
47.	betaLOC	54	The suffixes of this name pair have sufficient orthographic differences The third syllable sounds different. Betaconnect has an extra syllable.
48.	betaSERON	54	The suffixes of this name pair have sufficient orthographic differences The third and fourth syllable sound different
49.	BIPHetaMINE 12.5	54	When comparing Betaconnect to the root name Biphetamine, the prefixes and suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name Biphetamine, the first, second and fourth syllables sound different
50.	(b) (4)	54	When comparing Betaconnect to the root name (b) (4) the infixes and suffixes of this name pair have sufficient orthographic differences. When comparing Betaconnect to the root name (b) (4), the second, third and fourth syllables sound different. Betaconnect has two additional syllables.
51.	(b) (4)	54	The infixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. Betaconnect has an extra syllable.
52.	(b) (4)	54	The infixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. Betaconnect has an extra syllable.
53.	(b) (4)	54	The prefixes and suffixes of this name pair have sufficient orthographic differences.

			The first, second and third syllables sound different.
54.	etaNERCEPT	54	The prefixes, infixes and suffixes of this name pair have sufficient orthographic differences. The first, second and third syllables sound different.
55.	(b) (4)	54	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
56.	(b) (4)	54	When comparing the root name, the prefixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the first and third syllables sound different. Betaconnect has an extra syllable.
57.	(b) (4)	54	When comparing the root name, the prefixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the first and third syllables sound different. Betaconnect has an extra syllable.
58.	(b) (4)	55	The infixes and suffixes of this name pair have sufficient orthographic differences. The second and third syllables sound different. Betaconnect has an extra syllable.
59.	(b) (4)	55	The suffixes of this name pair have sufficient orthographic differences. The third syllables sound different. Betaconnect has an extra syllable.
60.	(b) (4)	55	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
61.	PENtacARINAT	55	The prefixes of this name pair have sufficient orthographic differences. The first, third and fourth syllables sound different. Pentacarinat has an extra syllable.
62.	(b) (4)	55	The prefixes and infixes of this name pair have sufficient orthographic differences.

			The first and second syllables sound different. Betaconnect has an extra syllable.
63.	(b) (4)	56	The infixes and suffixes of this name pair have sufficient orthographic differences. The second and third syllables sound different. Betaconnect has an extra syllable.
64.	CetacoRT	56	The suffixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. Betaconnect has an extra syllable.
65.	(b) (4)	56	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
66.	(b) (4)	56	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
67.	(b) (4)	56	When comparing the root name, the prefixes of this name pair have sufficient orthographic differences. When comparing the root name, the first syllables sound different. Betaconnect has an extra syllable.
68.	ABAtacEPT	57	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first syllables sound different.
69.	BERACTANT	58	The infixes and suffixes of this name pair have sufficient orthographic differences. The second and third syllables sound different. Betaconnect has an extra syllable.
70.	beta CAROTENE	58	The infixes and suffixes of this name pair have sufficient orthographic differences. The third and fourth syllables sound different. Beta Carotene has an extra syllable.
71.	(b) (4)	58	The infixes and suffixes of this name pair have sufficient orthographic differences. The third and fourth syllables sound different. Betamethacot has an extra syllable.

72.	(b) (4)	58	The infixes and suffixes of this name pair have sufficient orthographic differences. The third syllables sound different. Betaconnect has an extra syllable.
73.	betaPEN-VK	58	When comparing the root name, the infixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the third syllable sounds different. Betaconnect has an extra syllable.
74.	(b) (4)	58	The infixes and suffixes of this name pair have sufficient orthographic differences. The third syllables sound different. Betaconnect has an extra syllable.
75.	DEPacon	58	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first syllables sound different. Betaconnect has an extra syllable.
76.	BENICAR HCT	59	When comparing the root name, the prefixes, infixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the second and third syllables sound different. Betaconnect has an extra syllable.
77.	(b) (4)	59	The infixes and suffixes of this name pair have sufficient orthographic differences. The first and third syllables sound different. Betaconnect has an extra syllable.
78.	(b) (4)	60	When comparing the root name, the infixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the second and third syllables sound different. Betaconnect has an extra syllable.
79.	(b) (4)	60	The infixes of this name pair have sufficient orthographic differences. The third syllables sound different. Betaconnect has an extra syllable.
80.	(b) (4)	61	The infixes and suffixes of this name pair have sufficient orthographic differences.

			The third syllables sound different. Betaconnect has an extra syllable.
81.	tacLONEX	61	The prefixes and infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
82.	AtacAND HCT	62	When comparing the root name, the prefixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the first and third syllables sound different. Betaconnect has an extra syllable.
83.	(b) (4)	62	When comparing the root name, the prefixes of this name pair have sufficient orthographic differences. When comparing the root name, the first and second syllables sound different.
84.	beta-CARDONE	62	When comparing the root name, the infixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the third and fourth syllables sound different.
85.	betaTREX	62	The infixes and suffixes of this name pair have sufficient orthographic differences. The third syllable sounds different. Betaconnect has an extra syllable.
86.	(b) (4)	62	The prefixes of this name pair have sufficient orthographic differences. The first syllables sound different. Betaconnect has an extra syllable.
87.	(b) (4)	62	When comparing the root name, the prefixes and infixes of this name pair have sufficient orthographic differences. When comparing the root name, the first, second and third syllables sounds different. Betaconnect has an extra syllable.
88.	(b) (4)	62	When comparing the root name, the prefixes of this name pair have sufficient orthographic differences. When comparing the root name, the first syllable sounds different. Betaconnect has an extra syllable.

89.	BELAtacEPT	63	The infixes and suffixes of this name pair have sufficient orthographic differences. The third and fourth syllables sound different. Betaconnect has an extra syllable.
90.	(b) (4)	64	When comparing the root name, the prefixes and suffixes of this name pair have sufficient orthographic differences. When comparing the root name, the first and second syllables sound different. Betaconnect has an extra syllable.
91.	(b) (4)	64	The prefixes and suffixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. Betaconnect has an extra syllable.
92.	(b) (4)t	64	The infixes of this name pair have sufficient orthographic differences. The first syllables sound different. Betaconnect has an extra syllable.
93.	(b) (4)t	64	The prefixes of this name pair have sufficient orthographic differences. The third syllables sound different. Betaconnect has an extra syllable.
94.	(b) (4)	66	The suffixes of this name pair have sufficient orthographic differences. The third syllables sound different. Betaconnect has an extra syllable.
95.	(b) (4)	62	The infixes, prefixes and suffixes of this name pair have sufficient orthographic differences. The first and second syllables sound different.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤49%)

No.	Name	POCA Score (%)

1.	n/a	

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
1.	(b) (4)	50	Discontinued medication with no available generics.
2.	(b) (4)	50	Discontinued medication with no available generics.
3.	(b) (4)	50	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
4.	(b) (4)	50	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
5.	(b) (4)	50	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
6.	EMETE-con	50	Discontinued medication with no available generics.
7.	(b) (4)	50	Discontinued medication with no available generics.
8.	(b) (4)	51	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
9.	MetaTENSIN #2	51	Discontinued medication with no available generics.
10.	MetaTENSIN #4	51	Discontinued medication with no available generics.
11.	ACUTect	52	Discontinued medication with

			no available generics.
12.	(b) (4)	52	Discontinued medication with no available generics.
13.	(b) (4) E	52	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
14.	betaINE	52	Discontinued medication with no available generics.
15.	(b) (4)	52	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
16.	(b) (4)	52	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
17.	BENDectIN	53	Name identified in Drugs at FDA database Unable to find product characteristics in commonly used drug databases.
18.	(b) (4)	53	Discontinued medication with no available generics.
19.	(b) (4)	53	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
20.	BEAN EXTRACT	54	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
21.	BENOXINATE	54	Discontinued medication with no available generics.
22.	(b) (4)	54	Name identified in RxNorm database Unable to find product

			characteristics in commonly used drug databases.
23.	BIPHetaMINE 20	54	Discontinued medication with no available generics.
24.	BIPHetaMINE 7.5	54	Discontinued medication with no available generics.
25.	(b) (4)	54	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
26.	DIMetaNE-TEN	54	Discontinued medication with no available generics.
27.	(b) (4)	55	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
28.	(b) (4)	55	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
29.	(b) (4)	55	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
30.	(b) (4)	56	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
31.	(b) (4)	57	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
32.	(b) (4)	57	Discontinued medication with no available generics.
33.	(b) (4)	64	Name identified in RxNorm database

			Unable to find product characteristics in commonly used drug databases.
34.	(b) (4)	64	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
35.	(b) (4))	68	Name identified in RxNorm database Unable to find product characteristics in commonly used drug databases.
36.	(b) (4)	55	Discontinued medication with no available generics.

Appendix H: Names not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name	POCA Score (%)
1.	(b) (4)	50
2.	(b) (4)	50
3.	CEFACLOR CD	50
4.	(b) (4)	50
5.	DECITABINE	50
6.	DEPAKENE	50
7.	(b) (4)	50
8.	DESONATE	50
9.	(b) (4)	50
10.	(b) (4)	50
11.	(b) (4)	50
12.	FOSCARNET	50
13.	JEVTANA KIT	50
14.	LEVONEST	50
15.	(b) (4)	50

16.	MITE EXTRACT	50
17.	NESACAINE MPF	50
18.	NESACAINE-MPF	50
19.	NETUPITANT	50
20.	(b) (4)	50
21.	(b) (4)	50
22.	(b) (4)	50
23.	(b) (4)	50
24.	(b) (4)	50
25.	(b) (4)	50
26.	ROBITUSSIN AC	50
27.	(b) (4)	50
28.	(b) (4)	50
29.	VICODIN ES	50
30.	(b) (4)	50
31.	DEXAMPEX	51
32.	(b) (4)	51
33.	(b) (4)	51
34.	(b) (4)	51
35.	EPANED KIT	51
36.	(b) (4)	51
37.	(b) (4)	51
38.	(b) (4)	51
39.	ANTAGONATE	52
40.	DELATEST	52
41.	DELTASONE	52
42.	(b) (4)	52
43.	DEPAKOTE ER	52
44.	DESENEX	52
45.	(b) (4)	52
46.	DICLOFENAC	52

47.	DIENOGEST	52
48.	DIOVAN HCT	52
49.	ENTOCORT EC	52
50.	MASTIC DENT	52
51.	(b) (4)	52
52.	NASONEX	52
53.	(b) (4)	52
54.	STATOBEX-G	52
55.	(b) (4)	52
56.	TEKTURNA HCT	52
57.	(b) (4)	52
58.	VASOSTRICT	52
59.	(b) (4)	52
60.	(b) (4)	53
61.	(b) (4)	53
62.	DICOPAC KIT	53
63.	(b) (4)	53
64.	(b) (4)	53
65.	(b) (4)	53
66.	NEPAFENAC	53
67.	PEPSODENT	53
68.	TUSSIONEX	53
69.	DEPAKOTE	54
70.	(b) (4)	54
71.	(b) (4)	54
72.	DOSTINEX	54
73.	SCANDONEST	54
74.	STATOBEX	54
75.	(b) (4)	55
76.	CITANEST	56
77.	DELTA-CORTEF	56

78.	(b) (4)	56
79.	(b) (4)	56
80.	TEVETEN HCT	58
81.	VITAMIN C TR	58
82.	(b) (4)	60

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/s/

LOLITA G WHITE
07/06/2015

DANIELLE M HARRIS
07/06/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103471/S-5186

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Toure, Hamet

From: Toure, Hamet
Sent: Monday, September 14, 2015 5:37 PM
To: Vicki Chen
Cc: Lopez, Nahleen (FDA)
Subject: 103471-5186_FDA proposed labeling
Attachments: 103471-5186_FDA proposed labeling_091415_ Betaconnect IFU_Cleaned.doc; 103471-5186_FDA proposed labeling_091415_ Betaconnect IFU_Marked.doc; 103471-5186_FDA proposed labeling_ 091415_ Prefilled syringe IFU_Clean.doc; 103471-5186_FDA proposed labeling_091415_ Prefilled syringe IFU_Marked.doc; 103471-5186_FDA proposed labeling_091415_Medication Guide_Clean.doc; 103471-5186 _FDA proposed labeling_091415_Medication Guide_Marked.doc; 103471-5186_FDA proposed labeling_091415_Quick Start Guide_Clean.docx; 103471-5186_FDA proposed labeling_091415_Quick Start Guide_Marked.docx; 103471-5186_FDA proposed labeling_ 091415.doc

Dear Ms. Chen,

We refer to BLA 103471 and its supplemental application 5186. We have reviewed your proposed labeling and our comments and revisions are enclosed. For ease of review, we are providing clean and track-changes versions of the patient labeling documents.

Please accept tracked changes in all the documents and provide your revisions as new tracked changes.

We request your response at your earliest convenience.

Best regards,

Hamet Touré, PharmD MPH
CDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4202
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
hamet.toure@fda.hhs.gov

72 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 103471/S-5186

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Bayer HealthCare Pharmaceuticals Inc.
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981-0915

ATTENTION: Vicki Chen
Associate Director, Global Regulatory Affairs

Dear Ms. Chen:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received November 25, 2014, submitted under section 351(a) of the Public Health Service Act for Interfereon beta-1b.

We also refer to your correspondence, dated and received April 16, 2015, requesting review of your proposed proprietary name, Betaconnect.

We have completed our review of the proposed proprietary name, Betaconnect and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 16, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ermias Zerislassie, Safety Regulatory Project Manager

in the Office of Surveillance and Epidemiology, at (301) 796-0097. For any other information regarding this application, contact Rebecca Lopez, Regulatory Project Manager in the Office of New Drugs, at (240) 402-2659.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TODD D BRIDGES
07/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103471/S-5186

PRIOR APPROVAL SUPPLEMENT - ACKNOWLEDGEMENT

Bayer HealthCare Pharmaceuticals Inc.
Attention: Vicki Chen
Associate Director, Global Regulatory Affairs
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981-0915

Dear Ms. Chen:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA SUPPLEMENT NUMBER: 103471/S-5186

PRODUCT NAME: Betaseron (interferon beta-1b) Injection

DATE OF SUBMISSION: November 25, 2014

DATE OF RECEIPT: November 25, 2014

This supplemental application proposes the following change: update Instruction for Use with a statement "Optional Use of BETACONNECT Autoinjector."

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 24, 2015, in accordance with 21 CFR 601.2(a).

If the application is filed, the goal date will be May 25, 2015.

CONTENT OF LABELING

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

If you have questions, please contact Su-Lin Sun, PharmD, Regulatory Project Manager, by email su-lin.sun@fda.hhs.gov or by phone at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Senior Regulatory Project Manager
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SU-LIN SUN
12/18/2014