# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

***APPLICATION NUMBER:***

# 103471Orig1s5189

***Trade Name:*** BETASERON®

***Generic or Proper Name:*** interferon beta-1b

***Sponsor:*** Bayer HealthCare Pharmaceuticals Inc.

***Approval Date:*** 05/26/2017

***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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103471/S-5189

**SUPPLEMENT APPROVAL**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Resmi John, MD
Associate Director, Global Regulatory Affairs
100 Bayer Blvd., P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. John:

Please refer to your Supplemental Biologics License Application (sBLA), dated July 29, 2016, received July 29, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for Betaseron (interferon beta 1-b) lyophilized powder for subcutaneous injection 0.3 mg/vial.

This Prior Approval supplemental biologics application provides for optional use of the BETACONNECT autoinjector with the "myBETAapp" and "BETACONNECT Navigator" software applications.

## 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 based our review of the BETACONNECT Navigator on our assessment of the low potential risk to patients posed by the BETACONNECT Navigator's features and functionality. You are advised that future modifications to the BETACONNECT Navigator and myBETAapp may require a regulatory submission and a more in-depth FDA review depending on what the modifications are. In determining the appropriate regulatory submission for such changes, you should consider the potential impact of the modifications on the safety and effectiveness of the modified system, including the potential risk to patients posed by the modifications. For any modifications not addressed by the comparability protocol included in this application, please contact the Review Division for more information regarding the appropriate submission type.

## 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 patient labeling) 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 include 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 July 24, 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 — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103471/S-5189**." Approval of this submission by FDA is not required before the labeling is used.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

## 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 prescribing information 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 prescribing information, 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 LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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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.**

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/s/

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ERIC P BASTINGS
05/26/2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# LABELING

# BETACONNECT™ autoinjector

## Instructions For Use

Language: English

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Reference ID: 4102713

**Important Information about your BETACONNECT autoinjector:**

- **Only use prepared BETASERON® (interferon beta-1b) 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 the right way to use it from a healthcare provider.**
- **You may use myBETAapp, which is a software application (app) for people taking BETASERON that can be used alone or with the BETACONNECT autoinjector. Go to www.betaseron.com for more information.**
- **The BETACONNECT Navigator is software that can be used by healthcare providers who are caring for patients using BETASERON. For more information, call BETAPLUS® at 1-800-788-1467.**

**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.
- 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.

- If your BETACONNECT is connected to a computer USB port or is plugged in for charging, it cannot be used for injection. Charge the BETACONNECT at a temperature between 50°F to 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.

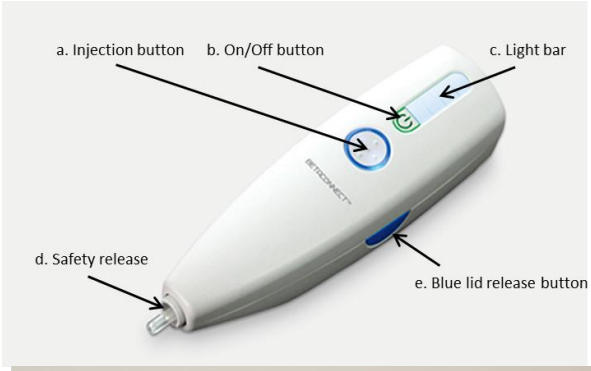
**Supplies needed for your BETACONNECT Injection**

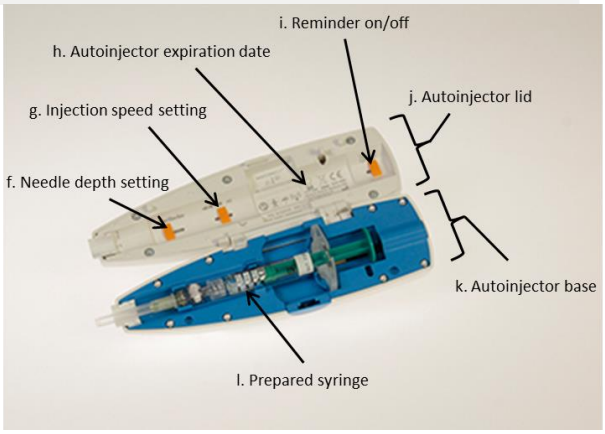
- BETACONNECT autoinjector
- prepared BETASERON syringe with attached capped needle (See Instructions for Use for BETASERON Prefilled Syringe)
- alcohol prep pad
- puncture resistant sharps container for throwing away used needles and syringes. (See "**Disposing of used needles and syringes**" at the 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), month (MM), and day (DD), printed as YYYY-MM-DD.

**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

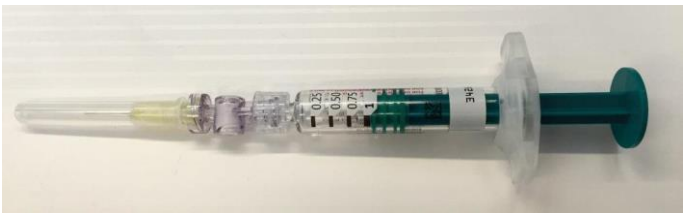
**l.** **Prepared syringe:** Use only the syringes that come with your BETASERON. Remember to refer to the BETASERON® (interferon beta-1b) Medication Guide for instructions on how to prepare your syringe. When you insert a prepared syringe, make sure that it is lined up with the syringe outline in the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

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

Charge the BETACONNECT at a temperature between 50°F to 95°F (10°C to 35°C). If your BETACONNECT is connected to a computer USB port or is plugged in for charging, it cannot be used for injection.

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


- Charging is complete when **all 4 green bars** are solid.
- When you disconnect BETACONNECT™ from the charger 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 autoinjector

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 solid 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 on-off button 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.

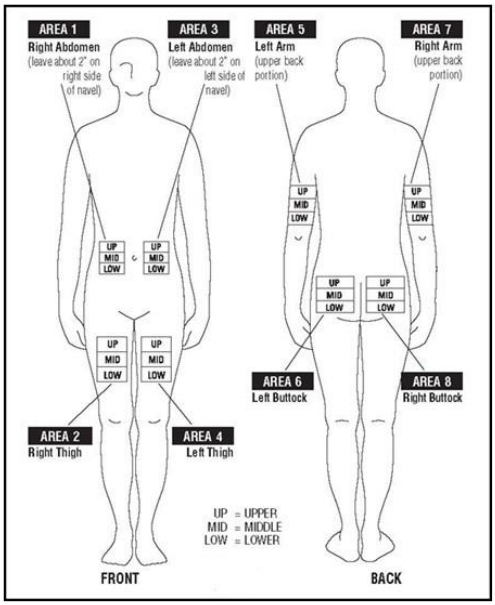
- The syringe must be lined up with the syringe outline.
- The lid will not close if the syringe is not seated properly.
- Check that your depth and speed settings are correct. (For depth and speed setting see chapter 4," Making Adjustments.")

Step 5: Close the lid and check the injection button


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

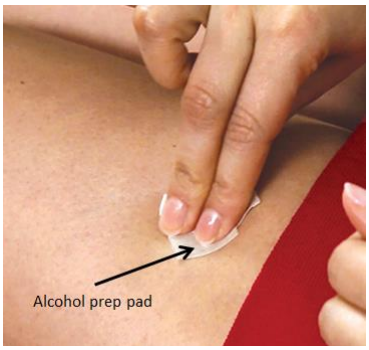
- When the injection button shows a steady blue light this means that BETACONNECT is now ready to be used for an injection.
- The lid must be fully closed to administer an injection.

### 3.2 Injection steps



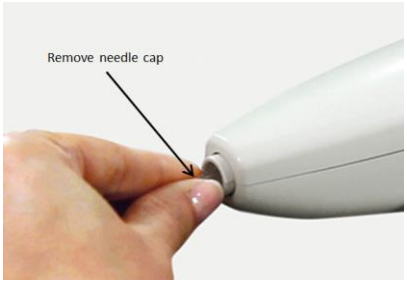

BETASERON is injected under the skin and into the fat layer between the skin and the muscles (subcutaneous tissue). The best areas for injection are where the skin is loose and soft and away from the joints, nerves, and bones such as the stomach (abdomen), upper arm, thigh or buttock. **Do not** use 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

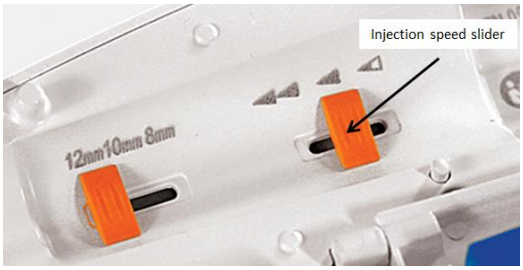

To adjust the injection depth:

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.

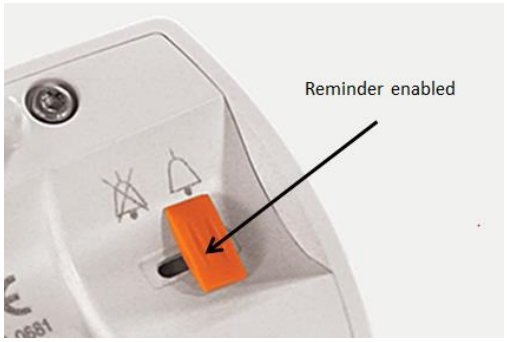
Step 2: Set the injection speed slider to the desired setting


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. |
| | 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** | 1. The BETACONNECT autoinjector will not operate | 1. Fully charge the BETACONNECT autoinjector |

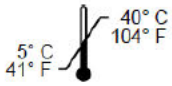
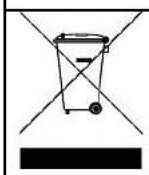
| Problem | Cause | Solution |
|---|---|---|
| **while it is being charged** | while it is being charged. | and remove the charger before use. |
| **Unable to use the BETACONNECT autoinjector while it is connected to a USB port** | 1. The BETACONNECT autoinjector will not operate while it is connected to a USB port. | 1. Disconnect the BETACONNECT autoinjector from the USB port. |
| **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 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, |

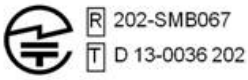
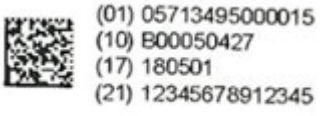
| Problem | Cause | Solution |
|---|---|---|
|  | | talk with your BETA Nurse or healthcare provider. |
| **An orange light is shown on the BETACONNECT autoinjector during charging** | 1. The temperature is too low or too high for charging. | 1. The BETACONNECT can be recharged at a temperature from 50°F to 95°F (10°C to 35°C). |

# Chapter 6: Technical Specifications

## 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), month (MM), and day (DD), printed as YYYY-MM-DD. 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.<br>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.<br>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.<br>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).<br>This device should not be modified (otherwise the granted designation number will<br>become invalid). |
|   | The Unique Device Identifier (UDI) that appears on the carton is shown by a barcode and human readable format:<br>(01): Device Identifier<br>(10): Batch Number<br>(17): Expiry date in YYMMDD format<br>(21): Serial number |

**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), month (MM), and day (DD), printed as YYYY-MM-DD. **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 (interferon beta-1b).

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

Manufactured for:
Bayer HealthCare
Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

U.S. License 1778



This Instructions for Use has been approved by the U.S. Food and Drug Administration 05/17

# myBETAapp™ Instructions for Use

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# 1 Overview of myBETAapp

myBETAapp is designed to assist you with managing your injections. It provides you with tools to record injection information and a calendar of your scheduled injections. myBETAapp includes the following features and functions:

1. Display scheduled injections according to the injection routine, i.e., one injection every other day.
2. Display suggested injection sites on the body, based on the injection sites shown in the full Prescribing Information for BETASERON® (interferon beta-1b).
3. Display a monthly calendar of recorded, missed, and scheduled injections.
4. Connect to BETACONNECT™ autoinjector via USB or Bluetooth, and transfer injection data recorded with the autoinjector. These injections will be displayed in the CALENDAR and INJECTIONS views.
5. Send a notice to record injection data to you via email.
6. Record indicators of health and wellness and summary of the information in a chart, for your personal use.
7. Allow you to share your injection history information with a BETA Nurse and your healthcare professional team, such as your doctor and your pharmacist.
8. Allows you to receive in-app messages from a BETA Nurse.
9. Export of injection history as a PDF document or as a CSV (comma separated value) file. This enables you to download and print out a copy of your injection history.

***The email notice to record injection data is independent of the injection reminder feature found on the BETACONNECT autoinjector. If you have the injection reminder switch enabled on your BETACONNECT autoinjector, you may get a reminder from the BETACONNECT autoinjector and a notice to record injection data from myBETAapp, at different times. Make sure that you only take your medication as prescribed by your physician.***

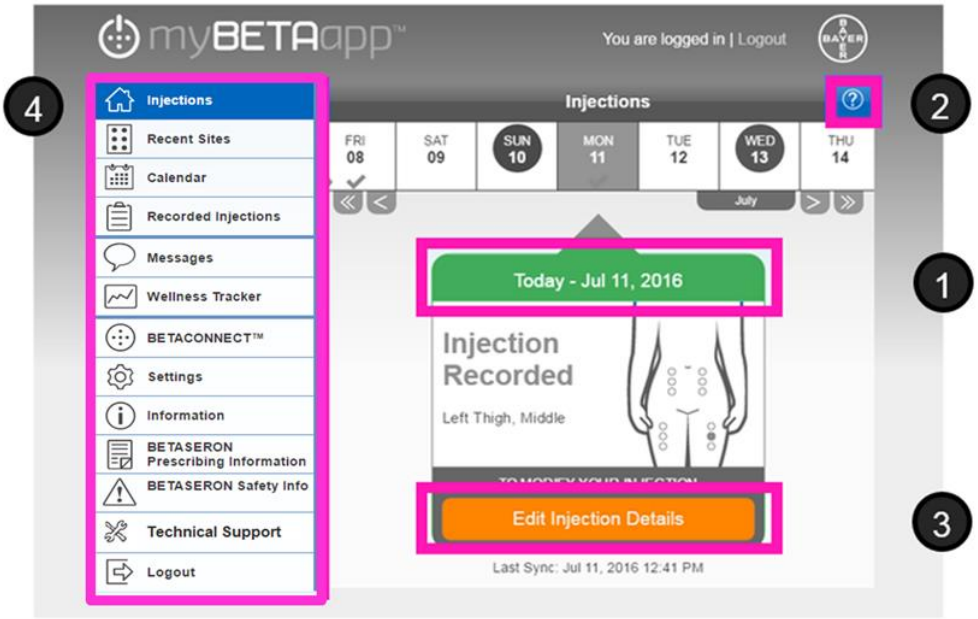


Reference ID: 4102713

***You must have an active internet connection to use myBETAapp. You do not need an internet connection to use the BETACONNECT autoinjector.***

# 2 myBETAapp User Interface

1. Colors: myBETAapp uses different colors and symbols in a consistent manner throughout the app:




myBETAapp uses three colors to represent injection activity:

**Green** indicates a recorded injection
**Red** indicates an injection not recorded
**Blue** indicates a scheduled injection

For example, you may see a diagram of the body showing various injection sites. The green color indicates sites where injections were recorded; the blue color indicates where injections are scheduled.

2. Icons: myBETAapp uses icons to indicate important functions. For example, the ⓘ icon always represents help or a legend describing what you see on the current screen.

3. Buttons: The buttons in myBETAapp are orange, with white text.

4. Menu: The main screens in myBETAapp are accessed via the MENU.



**For desktop and laptop computers:**

The MENU is always visible to the left of the main features.

**For smartphones and mobile devices:**

The MENU is hidden by default. Tap the icon in the top left corner of the screen to reveal the MENU. To hide the MENU, tap on the icon again.

# 3 Installing myBETAapp

To use myBETAapp, you must first install it on your computer or mobile device. You can find the latest information about obtaining myBETAapp for your system at www.betaseron.com

**For desktop and laptop computers:**

1. Download myBETAapp for Microsoft Windows or Apple Mac from www.betaseron.com.
2. Find the downloaded installer. If you do not know where to find the installer you downloaded, see "*Where can I find the myBETAapp installer that I downloaded on my computer?"* in Frequently Asked Questions.
3. Double-click the installer to begin the installation process. When prompted, select your language from the list of options.
4. Select an installation folder or select *Next* to accept the default location. Select *Finish* to complete the installation.

**For smartphones and mobile devices:**

Find a link for the app on www.betaseron.com or download and install the app from the Apple App Store (Apple iOS devices) or Google Play (Google Android devices).

***You should always use the newest version of myBETAapp. If a newer version is available, you will be asked to update or repeat the installation to install the newest version. Do not delete the current version you have on your computer or mobile device. Keep the current version and update it by downloading the most recent version.***

# 4 Launch and Configuring myBETAapp

## 4.1 Launching myBETAapp

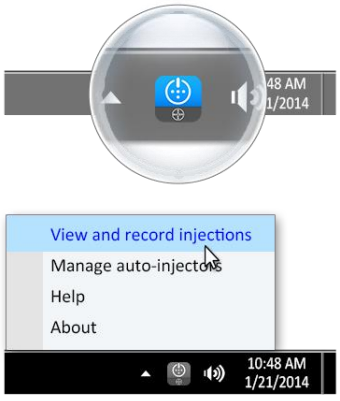
After you have installed myBETAapp on your computer or mobile device, you must launch the app to access its features.

Look for the myBETAapp icon.

**For desktop and laptop computers:**

Find and double-click the myBETAapp icon on your desktop to launch myBETAapp.

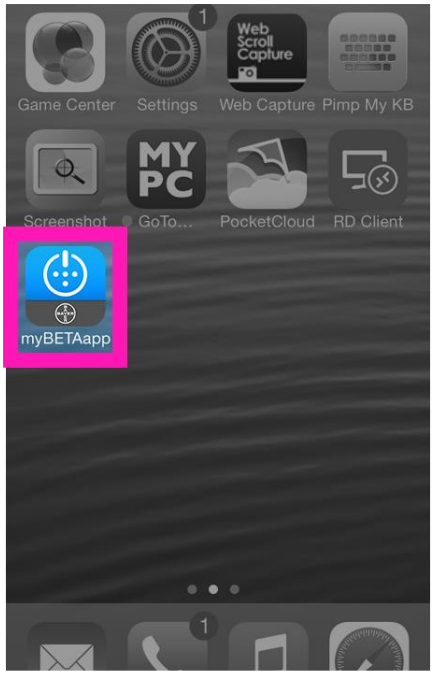
**Microsoft Windows**: You can also find the myBETAapp icon in your system tray. Click the icon and select *View and record injections* to access myBETAapp.




**Apple Mac**: You can also find the myBETAapp icon in the menubar at the top of the screen. Click the icon and select *View and record injections* to access myBETAapp.

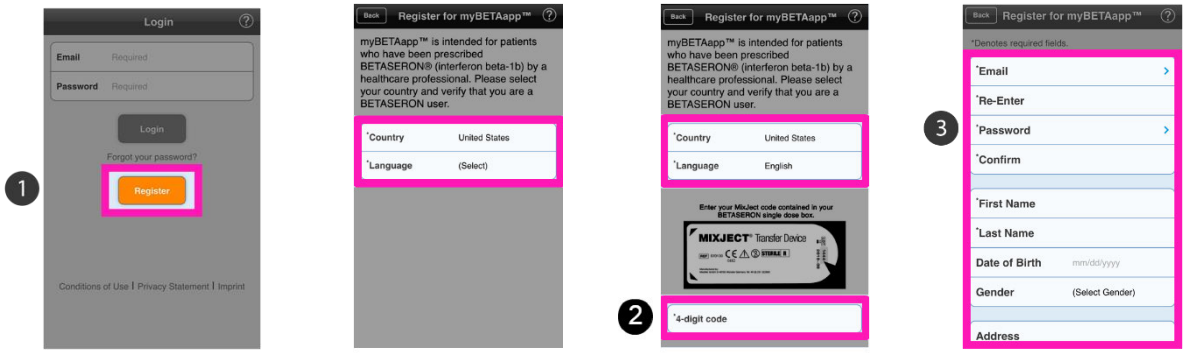
**For smartphones and mobile devices:**

Find and tap the myBETAapp icon on your screen to launch myBETAapp.




## 4.2 Registering for a myBETAapp Account

To use myBETAapp, you must log in with a user account and password. If you do not already have an account, you can register for one the first time you launch myBETAapp on your computer or mobile device.




1. When prompted to log in, select *Register* just below the login area. This will open a web browser on your computer or mobile device.

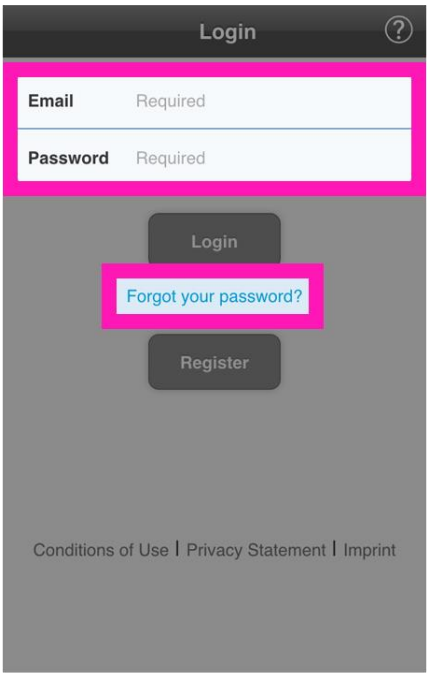
2. You will be prompted to enter a code from your BETASERON® drug packaging to continue the registration process. Please have a package of BETASERON® handy when setting up the app.

3. Provide the details requested on the registration screen. These details include your name, email address, a password that you will use to keep your account secure, and other contact information.

***You will receive an email to the email address you used for registration. It may take up to one (1) hour to receive the email message. You must select the link in the email message to activate your account. Until you do this, your account will not be active and you will not be able to use myBETAapp.***

## 4.3 Logging in to myBETAapp

To log in to myBETAapp, enter the email address and password you provided while registering.




If you do not provide a valid email address or password, myBETAapp will display an error message. You may re-enter the email address and password.

If you do not remember the password you used to set up your account, you may reset your password on the login screen. Refer to the Frequently Asked Questions for more details.

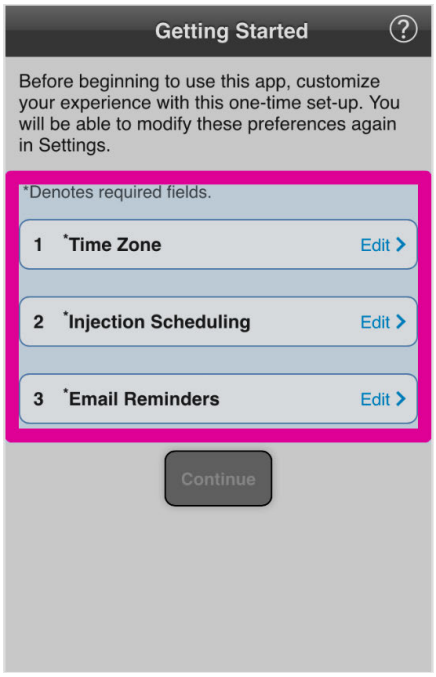
You must enter your email address and password at every login for security reasons. However, you can decide to let myBETAapp remember your login for 90 days if you prefer that. Refer to the Frequently Asked Questions for more details.

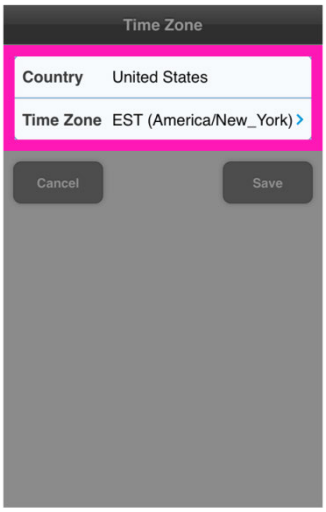
***When you log into myBETAapp you may be prompted to read and accept a disclaimer, product safety information, or other content before you can proceed.***

## 4.4 Configuring myBETAapp

When you log into myBETAapp for the first time, you will be presented with options to personalize your app experience. If you later wish to change your settings, you may do so using the SETTINGS screen.

Follow the on-screen prompts to configure myBETAapp. Options that you can configure include:



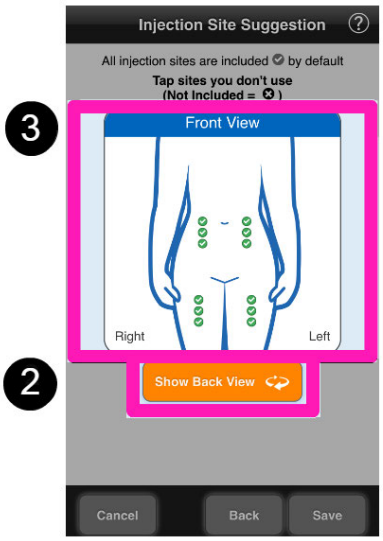

| | |
|---|---|
| Time Zone | Select *Time Zone* to set your time zone. The time zone you specify is used to send you a notice to record injection data at the correct time and to show recorded injections in local time. Remember to update the time zone when you travel.<br>  <br><br>Select *Save* to store your settings. |
| Injection Scheduling | Select *Injection Scheduling* to customize myBETAapp to your injection schedule and details.<br><br>**Setting Your Injection Schedule**<br>To provide you with an accurate calendar of scheduled injections, myBETAapp must know when you last injected or when you plan to inject. myBETAapp will schedule one injection every other day. |

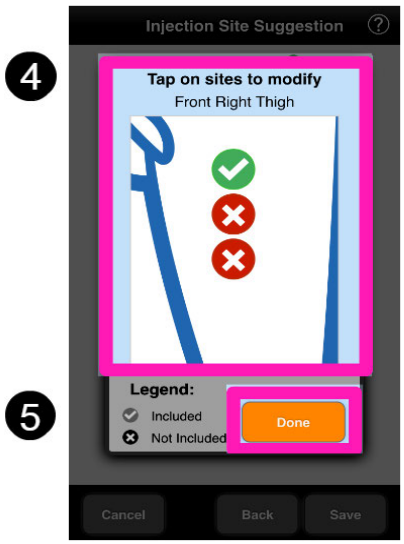
**If you have already started taking your injections**, select "Yes" when prompted:

1. Select *Last Injection Date* to select the date of your last injection.
2. Select your last injection site on the body diagram.
   a) Use the *Show Front View* button to show the front or *Show Back View* to show back of the body diagram.
   b) Select the region of the body containing your last injection site.
   c) In the enlarged portion of the diagram, select your last injection site. When you click or tap it, it will change to a green circle with white check mark (✓). This indicates that you have selected it as your last injection site.
   d) When you have finished selecting your last injection site, select *Done*.

**If you have not started taking your injections**, select "No" when prompted and then select the date of your first injection.

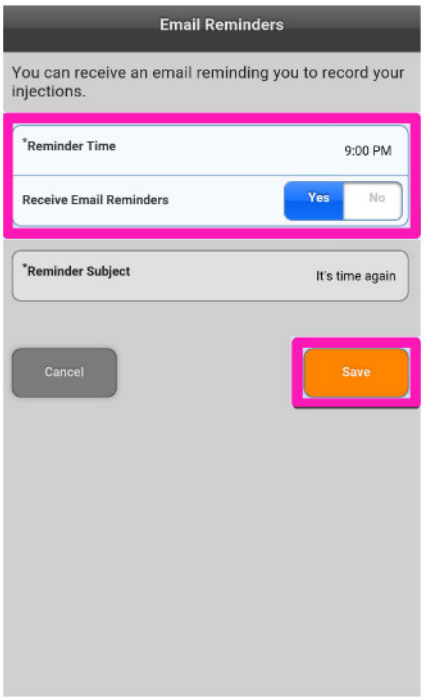
**Adjusting Next Injection Site Suggestion**
By default, all injection sites shown in the BETASERON® prescribing information are included.

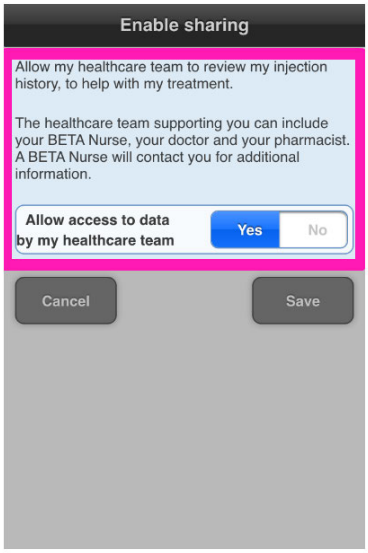



To adjust the sites that are included in your next injection site suggestion:

1. Select "Yes" when asked, "Do you want to customize your injection sites?"
2. Use the *Show Front View* button to show the front or *Show Back View* to show back of the body diagram.

| | |
|---|---|
| | 3. Select a region of the body containing the site or sites you wish to modify.<br><br>4. In the enlarged portion of the diagram, select a site you wish to change. When you click or tap it, it will change color as:<br><br>✅ Green with white check mark: The site will be included in the injection suggestions.<br>❌ Red with white X: Not included, this site will not be suggested.<br><br>5. When you have finished adjusting the sites in that region of the body, select *Done*.<br><br>6. Repeat for each region of the body for which you wish to customize the included suggested injection sites.<br><br>**You must include a minimum of two injection sites in your injection site suggestions.**<br><br>Select *Save* to store your settings. |
| Email Reminders | Select *Notice to record injection data* to configure injection data recording notifications, which will be delivered to you via email. This email is a helpful reminder to make sure your injection data is being recorded on a regular basis. See sections 8 and 9 of these instructions for guidance on how to record injection data<br><br>  <br><br><br>1. Indicate the time of day at which you typically take your injection. |

| | |
|---|---|
| | 2. Slide the toggle switch to *Yes* to enable email notifications.<br><br>3. If you do not wish to receive email notifying you to record injection, slide the toggle switch to *No* to disable email notifications.<br><br>4. Select *Reminder Subject* to edit the subject of the injection notification email you will receive.<br><br>Select *Save* to store your settings.<br><br>***The email notification is sent to the email address you use for login; remember to check your email frequently. You may change the email address in SETTINGS.***<br><br>***Reminders will not be available unless you have enabled sharing of your recorded injection history with your healthcare team.*** |
| Setting access to injection history data by your BETA Nurse and your team of Healthcare Professionals helping you with your treatment (your doctor and your pharmacist) | When you first set up the app, access to the injection history data by your healthcare team is already enabled.<br><br>A BETA Nurse coordinator will contact you to identify the correct physician and pharmacist who are supporting you with your BETASERON® treatment. If you later change your doctor or pharmacist, please contact your BETA Nurse at 1-800-788-1467 so the information can be updated.<br><br>Not all doctors or pharmacists will accept the data sharing arrangement. Your BETA Nurse will always participate in data sharing and will arrange for sharing with your doctor and/or pharmacist if they agree to participate.<br><br>If you for some reasons do not want to share your injection history data with the healthcare team, you can go to SETTINGS and disable data sharing.<br><br>From SETTINGS select *Share your recorded injection history with your healthcare team* to confirm if your injection history data is shared with your healthcare team.<br><br>  |

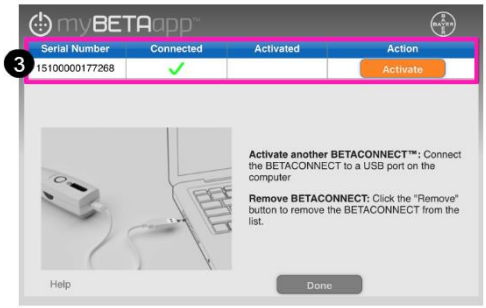
| | |
|---|---|
| | 1. If the toggle switch is in the "Yes" position, your injection history data will be shared with your BETA Nurse and the team of healthcare professionals supporting you with your treatment. If you do not want to share your injection history data with anyone, select the "No" position.<br><br>Select *Save* to store your settings.<br><br>***You can always go to SETTINGS and enable sharing of your injection history data again.*** |

# 5 Connecting BETACONNECT Autoinjector to myBETAapp

By connecting a BETACONNECT autoinjector to your account, historical injection data is automatically transferred from the autoinjector to myBETAapp. You can have one or more BETACONNECT autoinjectors connected and listed in myBETAapp. For each BETACONNECT autoinjector that you wish to connect to myBETAapp, follow these steps:

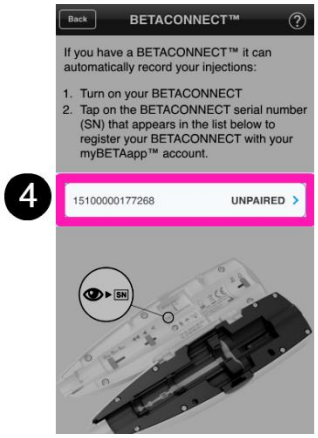
**For desktop and laptop computers:**

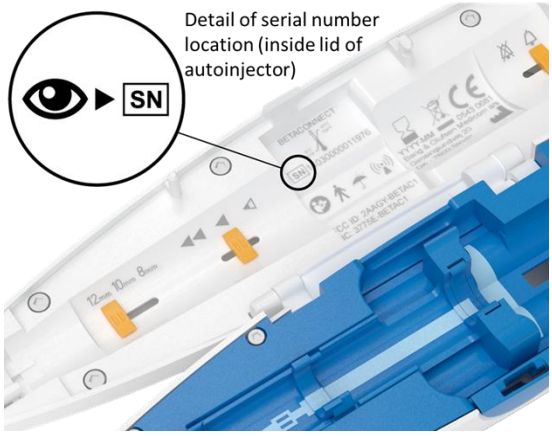
1. Connect your BETACONNECT autoinjector to one of the USB ports on your computer.
2. Login with your myBETAapp account.

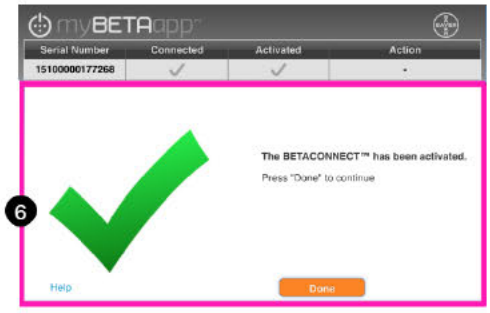




**For smartphones and mobile devices:**



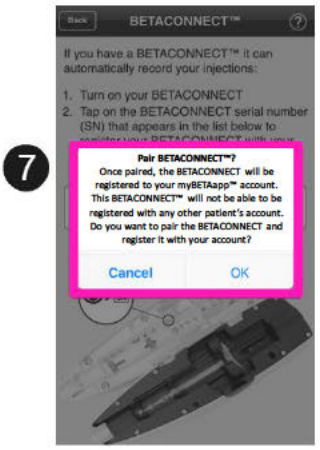






3. The serial number of your BETACONNECT autoinjector will appear in the list displayed on screen.
4. Compare the serial number with the serial number printed inside the lid of your BETACONNECT autoinjector to confirm that you are activating the correct device.
5. Select *Activate* to register the BETACONNECT autoinjector with your myBETAapp account.
6. Press *Done* to continue.

The injection data from the BETACONNECT autoinjector will be transferred automatically to your myBETAapp account whenever the BETACONNECT autoinjector is connected to a USB port on your computer. You do not need to open "Manage autoinjectors" for transferring data.

***You will not be able to make injections with a BETACONNECT autoinjector when it is connected to a USB port on your computer.***




1. Enable Bluetooth on your mobile device. Refer to the documentation for your mobile device for instructions and additional information about enabling Bluetooth.
2. Select the BETACONNECT screen from the MENU.
3. Power on your BETACONNECT autoinjector.
4. The serial number of the BETACONNECT autoinjector will appear in the list displayed on the screen.
5. Compare the serial number with the serial number printed inside the lid of your BETACONNECT autoinjector to confirm that you are activating the correct autoinjector.
6. Select the serial number of the BETACONNECT autoinjector you wish to register with your myBETAapp account.
7. When you see the confirmation message, confirm the registration by selecting *OK*.

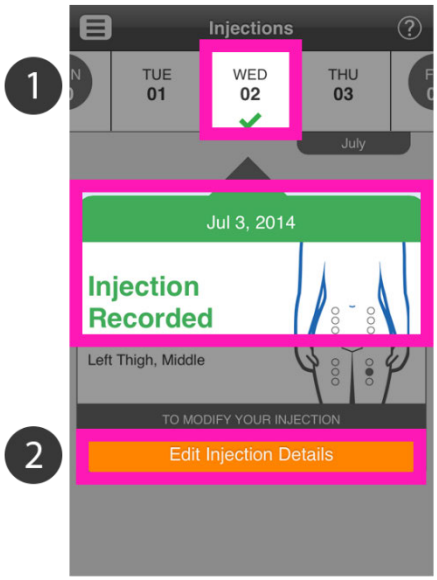
The injection data from the BETACONNECT autoinjector will be transferred automatically to your myBETAapp account whenever the BETACONNECT autoinjector is powered on and within range of your mobile device Important: myBETAapp must be open & running on your phone or device, in order for data transfer to occur.

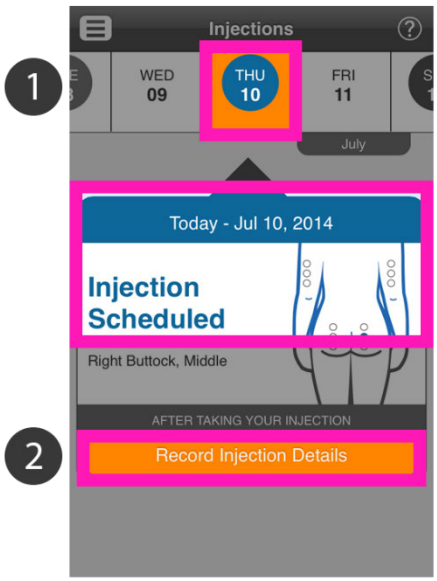
***myBETAapp will only interface to a BETACONNECT autoinjector, no other devices are supported.***

# 6 Determining when an Injection is Scheduled

There are two methods for viewing information about past and future injections in myBETAapp, from the INJECTIONS and CALENDAR views:

**Select INJECTIONS from the MENU:**




**Select CALENDAR from the MENU:**


1. Select the date of the injection you wish to view. The dates in the calendar are highlighted as follows:

    a. **Green** indicates a recorded injection.
    b. **Blue** indicates a scheduled injection.
    c. **Red** indicates an injection that was scheduled in the past and not recorded.

2. The date and injection site appear below the calendar.
3. Select the button containing the injection information to view details.
4. Select *Back* to return to the CALENDAR.


1. Select the date of the injection you wish to view. The injection details appear below the date and are color coded.

    a. **Green** indicates a recorded injection.
    b. **Blue** indicates a scheduled injection.
    c. **Red** indicates an injection that was scheduled in the past and not recorded.

2. To view additional details, select *Edit Injection*.

3. Select *Save* or *Cancel* to return to the INJECTIONS screen.

The details of each injection include date, time, and (if provided) injection site, dose, and note. If the injection was recorded automatically from a BETACONNECT autoinjector, the dose will be present and cannot be edited.

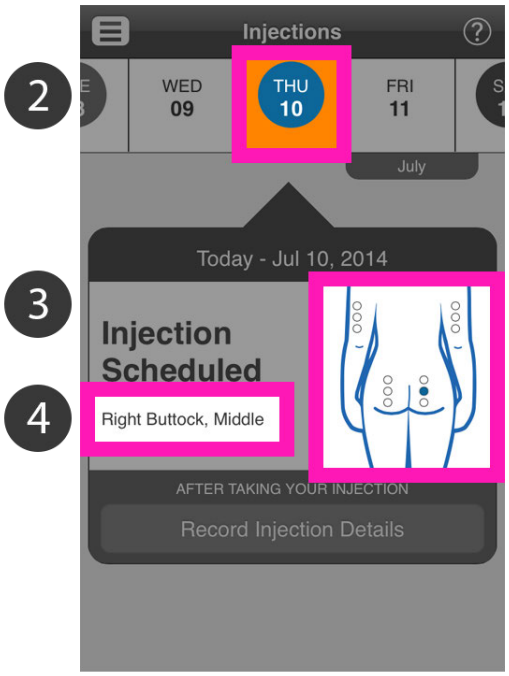
Three special icons may be shown on the INJECTIONS and CALENDAR views:
: The injection has been recorded after midnight and until 3am. The injection will be considered and displayed as belonging to the day before.

: An injection site has not been provided for the injection. You can add an injection site by selecting the injection and updating the injection details.

: Injections recorded both manually and automatically from the BETACONNECT autoinjector the same day. Injections performed with the BETACONNECT autoinjector should not be recorded manually.

# 7 Finding the Injection Site for a Scheduled Injection

To determine which injection site is suggested for a particular injection:




1. Select INJECTIONS from the MENU. The INJECTIONS screen shows, by default, today's scheduled injection, if there is one.
2. Select the date for which you wish to see the suggested injection site.
3. View the body diagram below the date. The body diagram shows a representation of the injection sites with the suggested site for this injection highlighted with a blue dot.
4. The suggested injection site is also described, in text, next to the body diagram. For example, you may see "right buttock, middle", indicating the suggested injection site is the middle part of your buttock on the right side of your body.

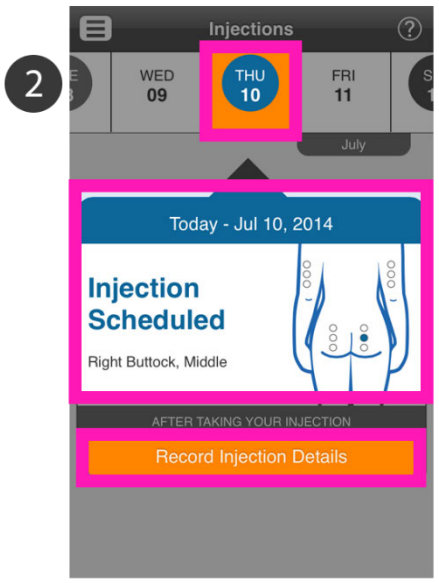
# 8 Recording an Injection Manually

If you do not have a BETACONNECT autoinjector or wish to record an injection that you performed with a syringe or other injection device, you can record the injection information manually.

**You cannot record an injection on a future date.**

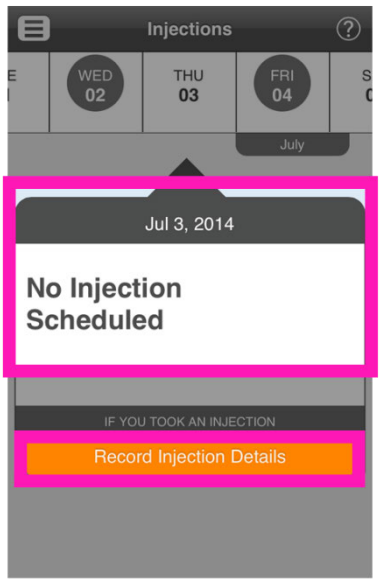
1. Select INJECTIONS from the MENU.
2. Select the date for which you wish to record an injection.

| **If there is already an injection scheduled on the selected date:** | **If there is no injection scheduled on the selected date:** |
|---|---|

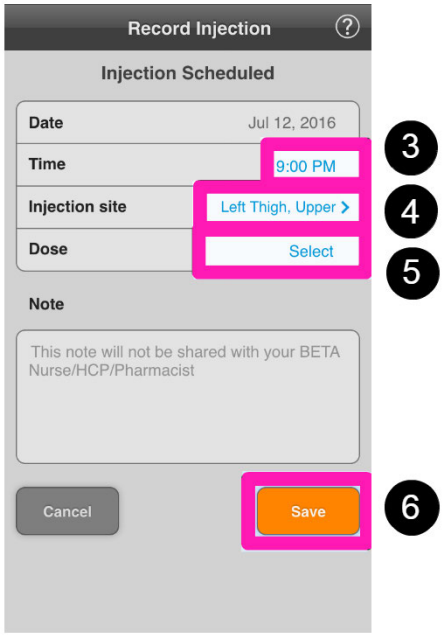




a. The details of the scheduled injection will appear below the selected date.
b. The body diagram will show the suggested injection site for the scheduled injection.
c. Select *Record Injection Details*.
d. Select *Record Manually* to record the injection.



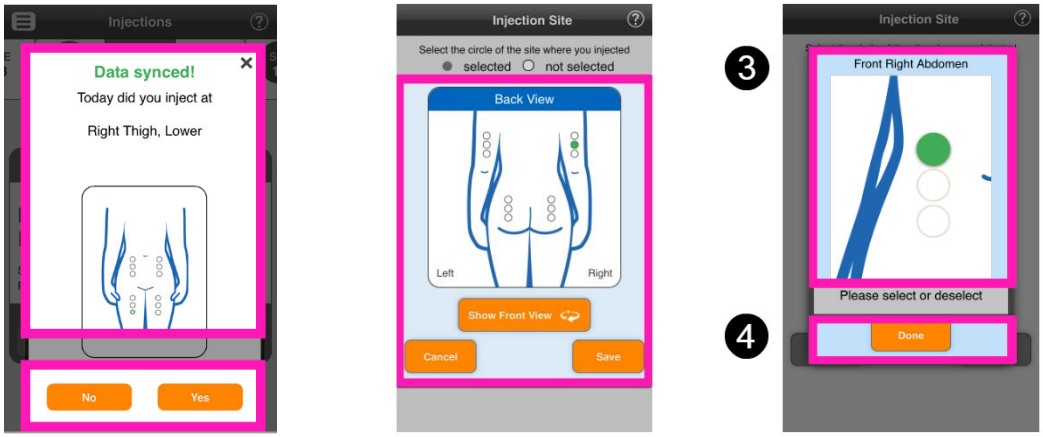

a. A message indicating that no injection is scheduled will appear in gray below the selected date.
b. Select *Record Injection Details*.
c. Select *Record Manually* to record the injection.




3. Enter the time the injection was performed.
4. Specify the injection site where the injection was performed:
    a. Select the name of the injection site to view a diagram of the body showing injection sites.
    b. Select the area of the body to display an enlarged view of the injection sites in that area.
    c. Select the injection site you wish to assign to the injection.
    d. Select *Done and Save*.
5. Select the injected dose from the options (0.25, 0.50, 0.75, or 1.0 mL).
6. Select *Save* to save the recorded injection details.

# 9 Recording an Injection with a BETACONNECT Autoinjector

**To record an injection automatically with a BETACONNECT autoinjector, first make sure your BETACONNECT autoinjector has been connected to myBETAapp (see Connecting BETACONNECT Autoinjector to myBETAapp).**



**For desktop and laptop computers:**

1. Launch myBETAapp to find the scheduled injection site.
2. Perform the injection with your BETACONNECT autoinjector.
3. Connect your BETACONNECT autoinjector to one of the USB ports on your computer.
4. Any recorded injections in your BETACONNECT autoinjector will be synchronized with your account. The screen will automatically update the status of any days where new injections were uploaded.
5. Verify that your injections were recorded successfully and if needed confirm or update the injection site.

**For smartphones and mobile devices:**

1. Launch myBETAapp to find the scheduled injection site (ensure Bluetooth is enabled on your mobile).
2. Perform the injection with your BETACONNECT autoinjector.
3. Any recorded injections in your BETACONNECT autoinjector will be synchronized with your account. The screen will automatically update the status of any days where new injections were uploaded.
4. Verify that your injections were recorded successfully and if needed confirm or update the injection site.

***After synchronization you will be prompted to confirm the injection site of your most recent injection. If you did not inject in the site presented, select No and follow the prompts to select the correct injection site.***

# 10 Logging Out of myBETAapp

To log out of myBETAapp, select LOGOUT from the MENU.

# 11 Troubleshooting and Frequently Asked Questions

**1. Where can I find the product ID, code, serial number, or PIN?**
The screen that prompts you for a product ID, code, DIN number, or PIN describes where you can find this information. In some cases, the product ID requested is located on the BETASERON® package. In other cases, you may have received a code or PIN from a healthcare professional. Follow the on-screen instructions carefully, as they may provide a telephone number to call for further assistance.

**2. Where can I find the myBETAapp installer that I downloaded on my computer?**
The myBETAapp installer can typically be found in the Downloads folder on your computer. For more information about downloads, see the appropriate reference for your web browser.

**3. Why do I need to register to use myBETAapp?**
Your injection data is stored in the cloud. You must register with an email address and private password to secure your data.

**4. Is my personal and medical information secure?**
Yes, your personal and medical data is secured with technical and procedural safeguards according to the regulations in your country, as described in the Privacy Statement.

**5. Which data can my healthcare team see if I enable sharing data?**
That depends on the data recording method you are using. If you record manually or you are using BETACONNECT autoinjector your BETA Nurse or healthcare professional will be

able to get information of your injection, e.g. injection date, , injection speed, needle depth and injection site.

**6. Do I have to enter my email address and password every time I access myBETAapp?**

By default you will need to use your email address and password everytime you log in to myBETAapp. myBETAapp will automatically log you out after 30 minutes of inactivity for security reasons. However, you can allow myBETAapp to remember your login, so you are logged in automatically without entering your email address and password everytime, for 90 days. This option is available in the LOGIN OPTIONS in SETTINGS in the MENU.

**7. I forgot my password. How can I retrieve it?**

If you do not remember the password you specified during registration, you may reset it from the LOGIN screen. Select *Forgot your password?* and follow the on screen prompts. You will receive an email message containing a link to reset your password. You will receive an email confirmation that your password has been changed.

**8. I forgot my username. How can I retrieve it?**

The username is typically your email address. If you do not remember your username/ email address you will have to contact your BETA Nurse or healthcare professional for assistance.

**9. I keep getting logged out of myBETAapp. How do I stay logged in?**

For security reasons, you cannot stay logged into myBETAapp indefinitely. You will have to re-enter your email address and password after 30 minutes of inactivity. However, you can allow myBETAapp to remember your login for 90 days in order to simplify the login if you prefer that – please refer to question 6 above.

**10. Can I install myBETAapp on more than one computer or mobile device?**

Yes, you can install myBETAapp on any number of computers or mobile devices as long as they are supported platforms.

**11. My BETACONNECT injections do not appear in myBETAapp. What should I do?**

Review the instructions in Recording an Injection with a BETACONNECT Autoinjector, above. In particular, ensure that your BETACONNECT autoinjector is powered on and connected to your computer (via USB) or mobile device (via Bluetooth). Ensure that myBETAapp is open & running on your device and that your device has an active internet connection. Note that Bluetooth must be enabled on your mobile device and your BETACONNECT autoinjector must be near your mobile device. If the problem persists, contact your BETA Nurse or healthcare professional.

**12. My computer or mobile device was lost or stolen. Can I still access my recorded injection history?**

Yes. Since your recorded injection history and other information is stored in the cloud, install myBETAapp on your new computer or mobile device and log in with your existing myBETAapp account. If you use a BETACONNECT autoinjector, you will need to reconnect it to myBETAapp (see Connecting BETACONNECT Autoinjector to myBETAapp).

**13. Why does my "suggested next injection site" function not include all of the injection sites?**

Confirm that you have not disabled any of the injection sites in the SETTINGS screen. If you have done so, the sites suggestion function will automatically skip any injection site that you deselected.

**14.I am no longer receiving email notifications to record injection data. What should I do?**

Confirm that email notification is enabled in the SETTINGS screen. Please note that reminders will not be available unless the option of sharing your recorded injection history with your healthcare team is also enabled. In addition, check your spam or junk email folder in your email account to ensure that notifications have not mistakenly been categorized as spam.

**15.Can I print my recorded injection history from myBETAapp?**

You can print your recorded injection history using the print feature in your browser on your computer. However, the list of recorded injections has not been formatted specifically for printing. Additionally, from the RECORDED INJECTIONS in the MENU you can export your injection history into a PDF document or a CSV file, which can be printed or shared further.

**16.How do I uninstall myBETAapp?**

To uninstall myBETAapp, follow the same process that you would use to remove other software or apps from your computer or mobile device. Note that uninstalling myBETAapp does not delete your myBETAapp account or your data. You can access your data by reinstalling myBETAapp or using it on a different computer or mobile device.

**17. How do I delete my myBETAapp account and all of my data?**

To delete your account and data, select SETTINGS from the MENU. Select *Delete Account* to delete your account and follow the prompts to confirm that you wish to take this action. Your account and data will be completely deleted.

**18. I received an error message. What should I do?**

Make a note of the error message, including any numeric code and description you see. Contact your BETA Nurse or healthcare professional with the details.

**19. If I miss a dose, how do I adjust a scheduled injection date to a different day?**

To reschedule the date of your next injection select CALENDAR from the MENU. From the calendar choose the day you want to take your next injection. The calendar will automatically shift future injection dates to be two (2) days after the new injection day you have set.

**20. How do I revise or delete manually recorded injection data?**

If you have manually recorded injection data in the app you can modify the details of the entry or delete the entry entirely.

Select CALENDAR from the MENU and choose the date of that past manually recorded injection. If you want to change any detail, choose the button at the bottom of the screen. After selecting this button, the screen will be displayed with the fields that can be changed (those are in blue font). Follow the on-screen prompts to change the details and save your changes.

To delete the entry entirely, choose the red "*Delete Injection*" button at the bottom of the screen.

**21. I am still having problems using myBETAapp. What should I do?**

In case the program is not responding you may try to restart the application or reboot your computer/mobile device. For myBETAapp technical support, please call 1-800-788-1467.

Manufactured By:

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

Manufactured for:

Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.
Whippany, NJ 07981

U.S. License 1778



CE



Rev. 6.00-en_US01

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# SUMMARY REVIEW

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Eric Bastings, MD. Deputy Director. |
| **Subject** | Division Director Summary Review |
| **NDA/BLA # Supplement #** | BLA 103471, Supplement 5189 |
| **Applicant Name** | Bayer HealthCare Pharmaceuticals, Inc. |
| **Date of Submission** | July 29, 2016 |
| **PDUFA Goal Date** | May 29, 2017 |
| **Proprietary Name / Established (USAN) Name** | Betaseron (interferon beta-1b) for injection |
| **Dosage Forms / Strength** | 0.3 mg of lyophilized powder in a single-use vial for reconstitution using a syringe pre-filled with diluent. |
| **Proposed Indication(s)** | Indication unchanged. Supplement under review concerns the myBETAapp smartphone application and the Betaconnect Navigator desktop software system |
| **Action** | Approval |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| CDTL | John Marler |
| OBP | Ralph Bernstein |
| Clinical | Larry Rodichok |
| CDRH | John McMichael |
| DMEPA | Ebony Whaley |
| DMPP | Sharon Williams |
| OPDP | Aline Moukhtara |
| DNP Labeling | Tracy Peters |

# 1. Introduction and Background

The supplement under review concerns the myBETAapp application and the Betaconnect Navigator desktop software system for use with the Betaconnect autoinjector. Betaseron can be administered using either a prefilled syringe, or the Betaconnect injection device for use with the prefilled syringe.

As discussed by Dr. Marler, the myBETAapp is for use on a mobile device or computer to function as an injection tracking, recording, and reminder tool, for use with the Betaconnect Autoinjector (using a Bluetooth capability of the Betaconnect).

The Betaconnect Navigator system is an internet browser-based product intended to allow healthcare providers to access and review injection data recorded by myBETAapp.

In this supplement, the applicant proposes labeling changes to the Betaconnect autoinjector labeling related to the myBETAapp application, and instructions for use of the myBETAapp application.

# 2. CMC/Device

The CDRH review team concludes that the myBETAapp application and BETACONNECT Navigator software are acceptable, and that the comparability protocol to be used to determine how future myBETAapp software changes will be reported to FDA and whether prior approval supplements are required is adequate.

Dr. Bernstein reviewed the applicant's risk assessment of the potential impact of the Bluetooth radio frequency electromagnetic radiation from the BETACONNECT autoinjector to the Betaseron drug product. He concludes that the reconstituted Betaseron drug product should not be adversely affected by exposure to the Betaconnect transmitter, and recommends approval of the supplement. Dr Bernstein however recommends that the applicant be asked to address (post-approval) the potential for the Betaconnect autoinjector's to generate heat through charging or expending energy in normal usage.

# 3. Nonclinical Pharmacology/Toxicology

N/A.

# 4. Clinical Pharmacology/Biopharmaceutics

N/A.

## 5. Clinical Microbiology

N/A.

## 6. Clinical/Statistical-Efficacy

N/A.

## 7. Safety

N/A.

## 8. Advisory Committee Meeting

An advisory committee meeting was not necessary for the review of this supplement.

## 9. Pediatrics

N/A.

## 10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 11. Labeling

As discussed by Dr. Marler, the human factors study for myBETAapp, myBETAapp labeling, changes to the current labeling, and the comparability protocol were reviewed by various FDA disciplines, but the Betaconnect Navigator was not reviewed in detail because it does not provide clinical decision support features and functionality that are expected to require alteration of health care providers, patient, or caregiver behavior.

Dr. Marler discusses that an issue related to the possibility of an extra dose of Betaseron if the user chooses to receive audible reminders from the device itself and email reminders through

myBETAapp has be carefully considered by the review team and not found to pose a significant risk, for reasons described in his memo.

## 12. Decision/Action/Risk Benefit Assessment

As all engineering, human factors, and CMC issues related to the myBETAapp smartphone application and the Betaconnect Navigator desktop software system have been adequately addressed, I will issue an approval letter for Supplement 5189.

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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.**

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/s/

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ERIC P BASTINGS
05/26/2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# OFFICER/EMPLOYEE LIST

**Officer/Employee List**
**Application: BLA 103471/S5189**

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Bastings, Eric
Bernstein, Ralph
Boam, Ashley
Fong, Steven
Gilbert, Susannah
Lopez, Rebecca Nahleen
Marler, John
Moukhtara, Aline
Nguyen, Quynh Nhu
Peters, Tracy
Rodichok, Lawrence
Stevens, Alan
Ware, Jacqueline
Williams, Marcia Britt
Williams, Sharon

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

## Betaconnect Autoinjector and Software - Labeling Supplement

| | |
|---|---|
| **Date** | May 26, 2017 |
| **Reviewer** | John Marler, MD |
| **Subject** | Cross-Discipline Team Leader Review |
| **BLA** | 103471, Supplement 5189 |
| **Applicant** | Bayer HealthCare Pharmaceuticals, Inc. |
| **Date of Submission** | July 29, 2016 |
| **Type of Submission** | Standard prior approval efficacy supplement labeling change with clinical data for smart phone application. |
| **Sponsor's Document Sequence Numbers** | eCTD 0166, 0167, 0172-0179. SDN 1223, 1237, 1255, 1262, 1264, 1265, 1276, 1287, 1311, 1319 |
| **PDUFA Goal Date** | May 29, 2016 |
| **Proprietary Names / Established (USAN) names** | Betaseron (interferon beta 1-b) |
| **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. |
| **Proposed Indication(s)** | Relapsing Multiple Sclerosis |
| **Recommended:** | Approval of labeling for BETACONNECT autoinjector and myBETAapp smartphone software with comparability protocol for software changes. |

# 1. Introduction

This cross-discipline team leader review recommends approval of a prior approval efficacy labeling supplement for an injection tracking system for Betaseron (interferon beta-1b) for the treatment of relapsing forms of multiple sclerosis when using the approved BETACONNECT autoinjector.

The proposed injection tracking system has three components. The **myBETAapp** is for use on a mobile device or computer to function as an injection tracking and recording and reminder tool for use with the **Betaconnect Autoinjector**, a device already approved by FDA but without implementation of the capability to connect by Bluetooth to myBETAapp. The **Betaconnect Navigator** system is an internet browser-based product intended to allow healthcare providers to access and review injection data recorded by myBETAapp. The requested labeling changes apply primarily to two documents: the existing Betaconnect autoinjector labeling and new instructions for use of myBETAapp. The sponsor did not submit labeling for the Betaconnect Navigator software.

**Review Team.**

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

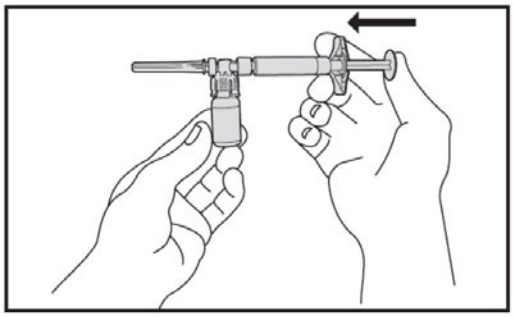
| Discipline | Reviewer | TL | Review |
|---|---|---|---|
| OBP | Ralph Bernstein | Cristina Ausin | Yes |
| DNP Clinical (Division of Neurology Products) | Larry Rodichok | John Marler | Yes |
| CDRH (Office of Device Evaluation) | John McMichael | Alan Stevens | Yes |
| Combination Products | | Patricia Love | |
| Office of Process and Facilities | Steven Fong | | |
| CDRH (Compliance) | Christopher Brown | | |
| CDRH (Office of Compliance) | Crystal Lewis | | |
| OSE RPM | | Darrell Jenkins | |
| DMEPA | Ebony Whaley | Lolita White | Yes |
| DMPP Patient Labeling (Med Guide PPI) | Sharon Williams | Marcia Williams | |
| OPDP (PI and Med Guide) | Aline Moukhtara | Mathilda Fienkeng | |
| DNP Labeling | Tracy Peters | | |
| RPM | Nahleen Lopez | Jackie Ware | |

# 2. Background

**Prior Approved Betaseron Labeling**. The recommended maintenance dose is 0.25 mg every other day. Dosage starts at 0.0625 mg (0.25 mL) every other day and

increases to the maintenance dose over a six week period. Betaseron is dispensed as a lyophilized powder in glass vials. It is sensitive to heat and stored in a refrigerator. The patient reconstitutes Betaseron by slowly injecting saline diluent into the Betaseron vial using the vial adapter (Figure 1). After reconstitution the patient must keep the reconstituted Betaseron cool prior to injection, which must occur within three hours.

**Figure 1 Betaseron Reconstitution with Vial Adapter**



The patient may choose to make the injection using the syringe directly or insert the syringe into the BETACONNECT autoinjector (Figure 2, and Figure 3). There are already approved Instructions for Use of the autoinjector that do not describe the injection tracking features.

**Figure 2 BETACONNECT Autoinjector**

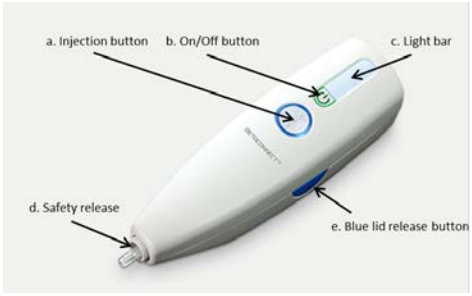
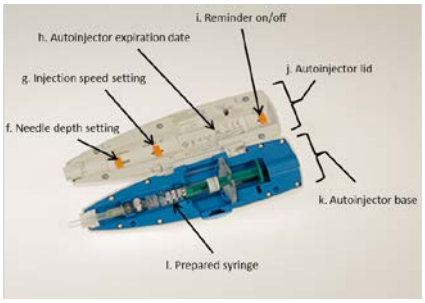



**Figure 3 BETACONNECT Autoinjector**




**Proposed Injection Tracking System.** If the patient uses the BETACONNECT autoinjector, the patient may choose to use myBETAapp installed on a mobile device or a laptop or desktop computer. Connection to a mobile device uses Bluetooth radio technology and connection to a computer is via wired USB connection. Data transferred from the autoinjector is stored on the local device and transferred by internet connection for remote data storage and backup. Once connected to myBETAapp, the patient may choose to allow access to the stored information by a caretaker through separate Betaconnect Navigator software on a remote computer to share information on aspects of treatment.

**Regulatory History.** FDA approved Betaseron (interferon beta-1b) on July 23, 1993. The current indication is relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. FDA approved The BETACONNECT Autoinjector on September 25, 2015 (Supplement 5186).

## 3. CMC/Device

Ralph Bernstein, Ph.D., performed the primary from the Office of Biotechnology Products, Division of Biotechnology Review and Research IV. Cris Ausin, is the Team Leader. The purpose of Dr. Bernstein's review is to evaluate the risk of the radio frequency electromagnetic (radiation) (RFEM) from the BETACONNECT autoinjector on reconstituted Betaseron. He concludes that "the Sponsor has provided an adequate risk assessment to allow the conclusion that reconstituted Betaseron DP should not be adversely affected by exposure to the RFEM in a theoretical worst case scenario when using the Betaconnect autoinjector." He recommends that from a CMC/quality perspective, the BETACONNECT autoinjector is approvable.

Dr. Bernstein noted there is a possible risk related to the effect of temperature from recharging the batteries or expending energy during normal use on the Betaseron drug product. This is potentially significant because Betaseron is temperature-sensitive. This issue will be addressed separately from this supplement.

## 4. CDRH Combination Product Consult

John McMichael, lead biomedical engineer, Lening Shen, software and cybersecurity consultant, and Alan Stevens, Branch Chief, prepared the CDRH review of the changes to the combination product consisting of the BETACONNECT autoinjector and device-associated software: myBETAapp and BETACONNECT Navigator.

CDRH reviewers sent information requests to the sponsor on three occasions. In each occasion the response was adequate. CDRH requested (b) (4) the Comparability Protocol to include the BETACONNECT Navigator software. The purpose of a comparability protocol is to determine how future software changes will be reported to FDA and whether prior approval supplements are required.

The CDRH review concludes that the software and cybersecurity measures are adequate for approval of the device constituent parts of the combination product. The Comparability Protocol, as modified by the sponsor in response to an information request, is adequate.

The CDRH review included summaries of the capabilities of each of the three device constituent parts of the BETACONNECT system.

BETACONNECT Auto-Injector:

The BETACONNECT device is an electronic re-usable autoinjector designed to use previously-approved disposable pre-filled piston syringes. Anticipated users are patients or care-providers 18 years or older, who nurses or other health care professionals determine are capable to make the injections using the device. There is no change in what users currently do prior to manual injection using the piston syringe. Users prepare the syringe, place the syringe in the device, select an injection site, and push a button. Built in software activates needle insertion, drug injection, post injection hold time, and needle retraction. There are three injection depth settings and three injection speed that users can select. There is also a visual and acoustic reminder function that can be disabled. The device stores information about each injection and can transmit it using a Bluetooth or USB connection to a mobile device or computer.

myBETAapp:

The myBETAapp is a stand-alone software product for optional use by patients or caregivers. MyBETAapp allows users to record injection data and choose and recall injection sites. The application can be installed on either a mobile device or a computer connected to the internet. The patient can enter injection data manually on the computer or mobile device, or the application can receive injection data stored in the BETACONNECT autoinjector through a USB or a Bluetooth connection. All information entered in myBETAapp is transferred to an external internet site. The patient may choose to enter additional health-related data and may choose to allow a healthcare provider to view the information through the BETACONNECT Navigator software

BETACONNECT Navigator

The BETACONNECT Navigator is software tool that communicates allows a patient-authorized healthcare provider to view the patient data stored remotely on the internet. The Navigator software presents injection data for review.

## 5. DMEPA Review of Human Factors Studies

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the human factors study for myBETAapp, myBETAapp labeling, changes to the current

labeling, and the Comparability Protocol. The DMEPA primary reviewer is Ebony Whaley, PharmD. DMEPA Team members included Team Leader Lolita White, PharmD; Associate Director for Human Factors, QuynhNhu Nguyen, MS; and Deputy Director, Irene Z. Chan, PharmD, BCPS.

DMEPA did not provide a review in depth of the BETACONNECT navigator because Betaconnect Navigator is an internet-based software application that collects therapy adherence data and provides secure internet-based platforms for HCPs [health care providers] and patients to record and share information on aspects of treatment but does "not provide clinical decision support features and functionality that are expected to require alteration of HCP, patient, or caregiver behavior."

One issue identified and resolved through interactions with the sponsor was the possibility of an extra dose if the user chose to receive audible reminders from the device itself and email reminders through myBETAapp. The level of concern was diminished when Bayer explained that alarm on the BetaCONNECT autoinjector resets itself after each injection and goes off 48 hours later. In addition, if the autoinjector records the injection event, no email reminder is sent. (b) (4) [redacted] The DMEPA review concludes that this change could provide an incremental layer of safety by allowing for ongoing monitoring by a provider. The conclusion of the DMEPA review is that <u>"no further human factors assessment of the myBETAapp email reminder use scenarios is needed, and Bayer may proceed with implementing this additional feature if they choose to."</u>

<u>DMEPA's conclusion is that "the revised myBETAapp app, revised myBETAapp IFU, and revised Betaconnect AI IFU are acceptable.</u>

Discussion of the Comparability Protocol which Bayer will use to determine how to inform FDA of any future changes in the BETACONNECT system components is ongoing at the time of this review.

## 6. Clinical/Statistical - Efficacy

Dr. Rodichok has reviewed Bayer's response to an information request regarding the safety of an accidental second injection of Betaseron submitted on March 10, 2017. He concluded that an additional injection was unlikely cause more than minor additional adverse events.

## 7. Safety

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

## 8. Advisory Committee Meeting

There was no advisory committee meeting for this submission.

## 9. Labeling

At the time of this review, the labeling is under negotiation with the. The key FDA recommendations for labeling changes relate to the instructions for use of myBETAapp.

## 10. CDTL Recommendations/Risk Benefit Assessment

I recommend approval for the BETACONNECT Navigator, myBETAapp, and the activation of the changes to the BETACONNECT autoinjector to allow Bluetooth connectivity with myBETAapp. The device has met CDRH engineering standards and meets usability-testing standards as reviewed by DMEPA. The risk of extra Betaseron injections due to reminders from the device and reminders by email have been carefully weighed by DMEPA and the clinical review team. 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.

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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.**

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/s/

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JOHN R MARLER
05/26/2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# CHEMISTRY REVIEW(S)

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

# MEMORANDUM

**Through**: Cris Ausin, Team Leader DBRR IV, OPQ, CDER
**From**: Ralph M. Bernstein, DBRR IV.
**Date**: 27 March 2017
**Re**: PAS BLA 103471 - eCTD sequence #0166.
**Product**: Betaseron, IFN-β, as indicated for RRMS.

**Purpose**:
The purpose of this supplement is to request approval of myBETAapp and BETACONNECT Navigator software. These software packages will be evaluated by ONP, CDRH and DMEPA.

The purpose of this review is to evaluate the Sponsor's risk assessment of the potential product quality impact of the radio frequency electromagnetic (radiation) (RFEM) from the Betaconnect autoinjector on reconstituted Betaseron.

**Sponsor:**
Bayer HealthCare
Pharmaceuticals Inc.
100 Bayer Blvd
P.O Box 915
Whippany, NJ 07981-0915
Phone: (862) 404-3000
Fax: (862) 404-3175 .

**Submitted:** 29 Jul 2016

**Recommendation:**
I recommend that from a CMC/quality perspective, this PAS is approvable. The Sponsor has provided an adequate risk assessment to allow the conclusion that reconstituted Betaseron DP should not be adversely affected by exposure to the RFEM in a theoretical worst case scenario when using the Betaconnect autoinjector.

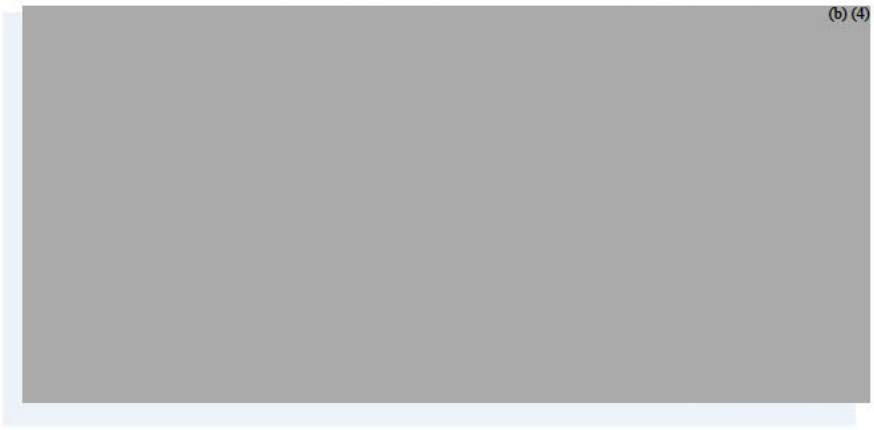
I do advise that a separate IR unrelated to this supplement's approval be sent to the Sponsor regarding the potential for the Betaconnect autoinjector's potential to generate heat through charging or expending energy in normal usage, potentially impacting reconstituted Betaseron product quality.

**Background**:
A PAS for the use of the BETACONNECT autoinjector along with the myBETAapp and [redacted] (b) (4) was submitted on 25 Nov 2014, and the Agency

requested that the Sponsor withdraw the myBETAapp and (b) (4) from the PAS at that time due to missing data. The BETACONNECT auto injector alone was approved for use with Betaseron on 25 Sept, 2015.

The purpose of the current supplement is to request approval of myBETAapp and BETACONNECT Navigator software. These software packages will be evaluated by ONP, CDRH and DMEPA. These are software packages that use an app on a phone or on a personal computer (myBETAapp) to remind users to take medication, track medication usage and to send that usage to the health care provider (BETACONNECT Navigator).

Figure 1-1. Data Transfer from BETACONNECT Autoinjector to myBETAapp




Briefly, the Betaconnect auto injector is a rechargeable battery powered autoinjector (see Figure 1-1, above) that the patient places a reconstituted Betaseron syringe into to allow for the use of an autoinjector. The Betaconnect auto injector has the ability to communicate through Bluetooth RFEM to a phone with the above mentioned app. The Betaconnect autoinjector can also connect to a computer using a USB connection.

This quality review will only address the response to the Agency's query (submitted 4 Feb 2016) to the Sponsor regarding RFEM and exposure to Betaseron. See question to Sponsor, below:

"You state that the BETACONNECT autoinjector utilizes Bluetooth technology to connect to a cellphone or computer through the myBETAapp. Your submission does not include any information regarding the potential effects of thermal and non-thermal effects of the radio frequency on the product quality. You should provide a risk assessment of the thermal and non-thermal effects of the radio frequency radiation used to transfer the autoinjector data via Bluetooth on critical quality attributes of reconstituted Betaseron."

**Information submitted:**
The Sponsor submitted a risk assessment that evaluates the potential thermal and non-thermal impact of the RFEM from the BETACONNECT Bluetooth transmitter on reconstituted Betaseron. The BETACONNECT transmitter is a Bluetooth (b) (4) device with a frequency of (b) (4) and a nominal and maximum power of (b) (4),

respectively. In this risk assessment, the Sponsor assumed as a worst case scenario that if "all radiation will be directed to the syringe with a projected surface area of approx. 1 square CM (cm2), then the maximal power density is in the range of (b) (4)

Potential for non-thermal effects: the BETACONNECT Bluetooth operates at (b) (4), and the "minimum quantum energy required for a non-thermal energy transfer to a water protein formulation corresponds to approximately 22 GHz" therefore the Sponsor concludes that as the Bluetooth energy is one magnitude lower than that of the 22 GHz needed to cause a non-thermal interaction there is no potential for product related impact..

***Reviewer comment:*** *The Sponsor has supplied literature that supports this assumption. E.g., See Uysal et al., DOI: 10.1109/RFID.2010.5467274 Conference: RFID, 2010 IEEE International Conference on RFID; Uysal I., Emond J.P.: RFID in the Pharmaceutical Supply Chain: Regulations, Physical Limitations and a Real-Life Study. RFID Journal Live Ninth Annual Conference and Exhibition, 2011, Orlando, FL, USA.*

Potential for thermal effects: the Sponsor states that thermal effects are theoretically possible, as opposed to non-thermal effects, as "increases in thermal absorption of RF by saline / protein solutions at frequency levels below 5 GHz have been documented." The Sponsor assumed RFEM at the thermal amount of two worst case potential scenarios: 1- "transmitting all injection data collected during the entire life cycle of the injector at once", or 2-"patients forgetting the prepared syringe in the injector leaving the drug being exposed to the energy as emitted during advertising mode over 20 minutes until the injector turns off automatically."

***Reviewer comment:*** *The Sponsor did not perform any experiments or use any analytical assays to examine the potential for impact on Betaseron. These are theoretical calculations based upon published literature.*

Table 4.3-1, below, outlines the amounts of energy expected to be emitted by the Bluetooth transmitter, in the worst case scenarios as stated above:

**TABLE 4.3-1 CHARACTERISTICS OF DIFFERENT USE SCENARIOS OF THE BETACONNECT BLUETOOTH TRANSMITTER**

| | Max. Power | Energy | Temperature increase | Exposure time |
|---|---|---|---|---|
| | (b) (4) | (b) (4) | | (b) (4) |
| Normal use | | | 0.00033 K | |
| Worst Case 1 First time use | | | 0.00085 K | |
| Worst Case 2 Advertising | | | 0.0042 K | |

***Reviewer comment****: The Sponsor states that their calculations indicate that the thermal increase of* $8.5x10^{-4}$ *K and* $4.3x10^{-3}$ *K when assumed to be completely absorbed by the protein are negligible. This assumption is supported by several studies, including the study referenced above, that examined quality attributes of biologics with 72 fold longer*

*exposure and 3000 times higher energy density. The Sponsor's conclusion that the RFEM emitted by the BETACONNECT Bluetooth enabled autoinjector should cause no harm to Betaseron, even in a worst case scenario, is acceptable.*

Draft IR to be sent to Sponsor regarding the potential for the Betaconnect autoinjector's potential to generate heat through charging or expending energy in normal usage:

Your Betaconnect auto-injector holds a syringe of reformulated Betaseron prior to and during the injection process. The Betaconnect auto-injector is rechargeable and contains battery and electrical components that may heat up when charging or that may give off heat when operating the auto injector. As reconstituted Betaseron is sensitive to heat, provide a risk analysis that addresses the effect of the heat produced by the auto-injector on the stability of the drug product. All risk mitigation strategies should be supported by data, such as the duration and intensity of temperature increases due to the charging and use of the auto-injector. If necessary, provide product quality data after preconditioning the final finished combination product (e.g. cyclic charging) and simulated use that mimics the worse foreseeable conditions (e.g. injecting during charging, injection immediately after charging, injection after multiple charging cycles). Provide a rationale for any test methods. Provide a rationale for the acceptability of any risk mitigations that include warning and/or caution statements with regard to the charging of the device and its impact on drug product quality.

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/s/

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RALPH M BERNSTEIN
03/27/2017

CRISTINA AUSIN-MORENO
03/27/2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# OTHER REVIEW(S)

OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

**GENERAL HOSPITAL DEVICES BRANCH**
**INTERCENTER CONSULT MEMORANDUM**

**CDER BLA 103471/S5189 – CDRH ICC1600540**

**Date**: May 22, 2017
**To**: Nahleen Lopez, PharmD
Division of Neurology Products (DNP),
Office of Drug Evaluation I (ODEI),
Office of New Drugs (OND),
Center for Drug Evaluation and Research (CDER)

**From**: John McMichael, Biomedical Engineer
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

**Through:** CDR Alan Stevens, Branch Chief
CDRH/ODE/DAGRID/GHDB

**Subject**: Review of PAS for myBETAapp and BETAConnect Navigator software

**Recommendation: Device Constituent Parts are Approvable**

| | |
|---|---|
| **Applicant** | Bayer |
| **Indication for Use** | BETASERON 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. |
| **Drug Constituent** | Betaseron (interferon beta-1b) |
| **Device Constituent** | BETACONNECT Autoinjector; myBETAapp, and BETAConnect Navigator |

| **Digital Signature Concurrence Table** | |
|---|---|
| Reviewer Sign-Off | |
| Branch Sign-Off | |

## I. Purpose

CDER/OND/ODEI/DNP has requested CDRH/ODE's assistance in providing a review of the myBETAapp and BETAConnect Navigator software that is associated with the BETACONNECT Autoinjector already approved under BLA 103471.

This memo provides a review of device constituent parts of the combination product under BLA 103471/S5189.

## II. Background/Previous CDRH Interactions

CDRH has participated in previous Type C Meeting requests in regards to the myBETAapp and BETAConnect Navigator software prior to submission of the Prior Approval Supplement that is the subject of this consultant review memo. Previous CDRH/ODE consultant memos can be found under ICC1500648 and in DARRTS.

This memo is a review of the device constituent parts of the Prior Approval Supplement, which includes the myBETAapp and BETAConnect Navigator software. The BETACONNECT autoinjector was previously approved under BLA 103471. CDRH/ODE was consulted for approval of the BETACONNECT autoinjector under BLA 103471.

This review does not consider the human factors regarding the myBETAapp or BETAConnect Navigator software, which is covered by CDER/OSE/DMEPA review.

## III. Documents Reviewed

- BetaConnect Lifecycle [redacted]
- Comparability Protocol
- Comparability Protocol v2
- Response to FDA Info Request Dated 24Jan2017
- myBETAapp Risk Management Report
- Response to FDA Info Request date 10Nov16
- Response to FDA Info Request Dated 28Sep2016
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted] Device Description - Autoinjector [redacted]
- Response to FDA Info Request Dated 29Aug2016
- Design Risk Analysis - [redacted]
- LoA [redacted] (BETAapp)
- LoA [redacted] (BETAapp)
- Device Description - [redacted]
- Device Description - [redacted] 1
- [redacted] Navigator Risk Management Report v.2.10
- [redacted] myBETAapp Risk Management Report v.3.10
- [redacted] - Navigator Residual Anomalies v1.00
- [redacted] - myBETAapp Residual Anomalies v1.00
- [redacted] - Software Maintenance Plan - [redacted]
- [redacted] Architecture and Interface Specifications - ver. 2.00
- [redacted] - [redacted] 6.00
- [redacted] - Development Environment Description v1.00
- [redacted] - [redacted]
- [redacted] - [redacted]

## IV. Review Team

| Review Team Member | Team Member Role |
|---|---|
| John McMichael | Lead Reviewer |
| Lening Shen (CDRH/ODE/DAGRID/GHDB) | Software / Cybersecurity Consultant |

## V. Combination Product Description (taken from BLA 103471)

The combination product description has been further divided into the drug product and the device description.

**Drug Product Description:**
**Current Name:**
Betaseron

**Dosage Form:**

Injection

**Route of Administration:**
Subcutaneous

**Dosing Regimen:**
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

**Device Description:**
The following was provided by the Sponsor:

The BETACONNECT autoinjector is an optional automatic Betaseron injection device that stores data related to the use of the device (date of injection, injection speed selection, injection depth selection and injection volume).

Injection data can be manually recorded into the myBETAapp by the patient or transmitted from the autoinjector through either a USB cable or a Bluetooth connection to a computer/smartphone by use of the myBETAapp.

All data recorded in the myBETAapp will be transmitted through the internet to a secured cloud-based database.

If accepted by the patient, HCPs can have access to these data and monitor the injection activities of the patient and communicate with the patient (i.e. by sending predefined messages to them via the app) or otherwise initiate a discussion with the patient, to assist the patient with their therapy.

The patients have access to their own data via myBETAapp in which they can monitor past injections.


## VI. Device Constituent Parts

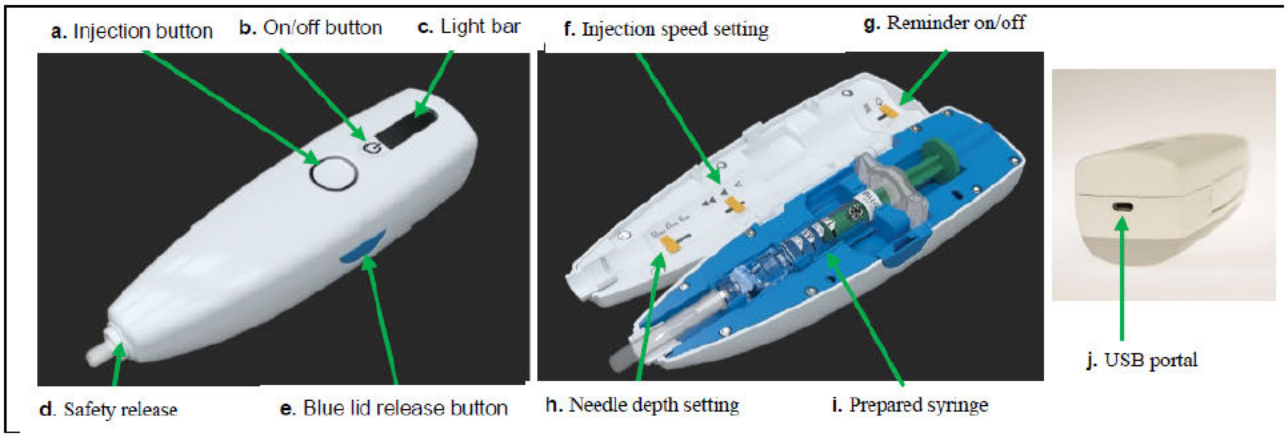
BETACONNECT Auto-Injector:
The BETACONNECT™ is an electronic re-usable autoinjector designed for use with disposable pre-filled piston syringes.

The BETACONNECT™ is designed to be used by patients or care-providers 18 years or older, who have been found capable by nurses / health care professionals to operate the BETACONNECT for injections.

Use of the BETACONNECT™ would be an alternative option for users to inject BETASERON®; there is no change in what users currently do prior to manual injection using the piston syringe. Users simply insert the prepared syringe in the BETACONNECT™ and by a push of a button the injection is performed automatically. The built in firmware activates needle insertion, drug injection, post injection hold time and needle retraction.

The three injection depth settings and three injection speed settings on the BETACONNECT™ allow users to select the ones most suited for them. There is also a convenient visual and acoustic reminder function that can be disabled.

Below is an image of the BETACONNECT Autoinjector with particular features highlighted:




**myBETAapp: (taken from** [redacted] (b) (4)

The myBETAapp is a stand-alone software product for optional use by patients/caregivers as part of each patient's Betaseron therapy. The purpose of the myBETAapp software is to help patients/caregivers monitor the treatment prescribed by the patient's physician. **The myBETAapp can help patients/caregivers track injection data and allow users to configure and track the injection sites.** The patient can manually enter information into myBETAapp or transmit injection data stored in the BETACONNECT autoinjector through USB or Bluetooth connection. The Patient has the option of entering personal wellness information. If the patient enabled third party access to the injection information, **HCPs can view these data via another stand-alone software product (BETACONNECT Navigator).** The myBETAapp is available as Android and IOS mobile app and Windows and [redacted] (b) (4) desktop version.

**The myBETAapp can provide email reminders to the patient for future scheduled injections (can only be scheduled every other day after the last injection in accordance with the intended dosage/administration of Betaseron)**. myBETAapp can also show a calendar view of all past and future scheduled injections with associated information regarding the following:

1) Time/date of injection
2) Dose size
3) Needle depth
4) Injection speed
8) Injection notes (if added by user)
9) Injection site (if added by user)

**The completed (history) and scheduled injection** [redacted] (b) (4)

Injection recorded: Green mark
Missed injection: Red mark
Scheduled injection (next injections): Blue mark

[redacted] (b) (4)

**There must be** [redacted]. The marks must be colored as:

[redacted]
Past injection sites: Green [redacted]
[redacted] proposed injection site: Blue [redacted]

Left and right on body diagram must be clearly stated (where only one side is shown). The purpose of the injection site configuration must be stated to the user.

All application requirements and specific functionalities are detailed in the Product Requirements version 6.00 in [redacted].

[redacted]

**BETAConnect Navigator: (taken from [redacted])**
The BETACONNECT Navigator [redacted]

[redacted] BETACONNECT Navigator, [redacted] **myBETAapp**. From the BETACONNECT Navigator [redacted]

It must be possible to view [redacted]:
[redacted]

(b) (4)

**The HCP(s) can** (b) (4)

All application requirements and specific functionalities are detailed in the (b) (4) version 6.00 in (b) (4).

(b) (4)

## VII. CDRH/ODE Review

The following is a summary of the review conducted by CDRH/ODE in assessing the adequacy of the information provided to support the changes as they relate to the device constituent parts of the combination product.

The software consultant, Lening Shen (CDRH/ODE/DAGRID/GHDB), performed a review of the myBETAapp and BETAConnect Navigator software and cybersecurity. The information reviewed included (b) (4) and (b) (4) for which the BLA holder Bayer provided an LOA for each Master File review.

After receiving responses to the information requests found in Section VIII, the software consultant recommended that the information provided related to the software and cybersecurity was adequate for approval of the device constituent parts of the combination product. **The Lead Reviewer did not concur with this recommendation and requested further information to accommodate a Moderate Level of Concern for the software applications.**

Below is a brief overview of the information and recommendations of the software consultant:

| | |
|---|---|
| 1. | Level of Concern - **Minor level of concern** for both the MyBETAapp and BETACONNECT Navigator since the software only captures and transmits data. It appears that there is no analysis or action taken based on the data. – **adequate.** |
| 2. | Software Description – including functions and screen shots. - **adequate** |
| 3. | Device (including software) Hazard Analysis – the device uses wireless communications. The sponsor did provide its cyber security considerations in the hazard analysis. - ***adequate*** |

4. Software Requirements Specifications (SRS) - ***adequate***
5. Architecture Design Chart – Not required. - ***adequate***
6. Software Design Specification – not required. - ***adequate***
7. Traceability Analysis - ***adequate***
8. Software Development Environment Description – not required. - **adequate**
9. Verification and Validation Documentation – detailed test case provided. - ***adequate***
10. Version History Log - ***adequate***
11. Unresolved Anomalies (bugs) – not required. – **adequate**
12. Cyber security – the sponsor systemically addressed according to our guidance document, including risks and mitigation in hazard analysis, specifications and design documents. – ***adequate***

**Lead Reviewer Comment:**
**The lead consultant reviewer does not concur with the conclusion of the software consultant that the Level of Concern is Minor. Instead the lead reviewer believes the Level of Concern to be Moderate based upon the functionality of the applications.**

**Below is the information provided by the Sponsor that reflects the correct Level of Concern and associated software documentation.**

1. Level of Concern - **MODERATE Level of Concern** for both the MyBETAapp and BETACONNECT Navigator since the software captures/transmits data and provides injection reminders to the patient.
   **Lead Reviewer Recommendation: Adequate**

2. Software Description – including functions and screen shots.
   **Lead Reviewer Recommendation: Adequate**

3. Device (including software) Hazard Analysis – the device uses wireless communications. The sponsor did provide its cyber security considerations in the hazard analysis.
   **Lead Reviewer Recommendation: Adequate**

4. Software Requirements Specifications (SRS)
   **Lead Reviewer Recommendation: Adequate**

5. Architecture Design Chart
   **Lead Reviewer Recommendation: Adequate**

6. Software Design Specification
   **Lead Reviewer Recommendation: Adequate**

7. Traceability Analysis
   **Lead Reviewer Recommendation: Adequate**

8. Software Development Environment Description
   **Lead Reviewer Recommendation: Adequate**

9. Verification and Validation Documentation – detailed test case provided
   **Lead Reviewer Recommendation: Adequate**

10. Version History Log
**Lead Reviewer Recommendation: Adequate**

11. Unresolved Anomalies (bugs) and associated risk analysis
**Lead Reviewer Recommendation: Adequate**

12. Cyber security – the sponsor systemically addressed according to our guidance document, including risks and mitigation in hazard analysis, specifications and design documents.
**Lead Reviewer Recommendation: Adequate**

After updating the Comparability Protocol in response to information requests, the Sponsor's Comparability Protocol regarding future updates to the myBETAapp and Navigator software device constituents is adequate.

The Sponsor provided a risk assessment associated with the thermal and non-thermal effects of the Bluetooth Transmitter on the drug product Betaseron. This information was reviewed by CDER/OPQ and found to be adequate. This information is not considered a part of this review memo as it was not under the review of the CDRH/ODE reviewer.

## VIII. Information Requests Sent on 08/29/2016

**For BLA Sponsor (Bayer Pharmaceuticals):**

1. Please be advised that the Agency has communicated deficiencies regarding content found within (b) (4) and (b) (4) directly to the master file holder. The Agency is unable to provide details of these deficiencies to you as the documentation is not contained directly within the BLA. Approval of the BLA prior approval supplement depends on resolution of the deficiencies communicated to the master file holder. Please work with the master file holder to resolve these concerns and provide responses to (b) (4) and (b) (4) record. Alternatively, and if appropriate, you may provide responses to these questions and supporting documentation to the BLA record.

**Sponsor Response:**
See responses to further information requests.

**For (b) (4) and (b) (4) holder (b) (4)**

The following deficiencies apply to the MyBETAapp and BETACONNECT devices held under (b) (4) and (b) (4), respectively:

1. (b) (4)

(b) (4)

.

**Sponsor Response:**

Bayer, (b) (4), has addressed the threats of cybersecurity in a systemic fashion as required by the FDA guidance document "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" dated October 2, 2014 during the design of the BETACONNECT autoinjector and associated myBETAapp and BETACONNECT Navigator. In response to the Agency's request, the primary concern for these devices is information security. These risks have been evaluated and included in our risk assessments with any risks mitigated and verified or validated. The documentation generated is part of the Design History File for these products.

In order to facilitate the FDA's review, (b) (4) has summarized the specific assessments and activities that have been implemented to address cybersecurity concerns in the document – "Cybersecurity Analysis" (b) (4) which has been submitted to the (b) (4) and (b) (4) (b) (4), respectively). This document identifies the entire list of potential vulnerabilities, provides the reference in the risk documentation that summarizes and justifies the mitigations and identifies the software requirements where these mitigations are implemented, which are traceable to the design verification report chapter "6.1 System Test Review" already provided. It also provides the plan for providing validated software updates and patches as needed throughout the lifecycle of the medical device to continue to assure its safety and effectiveness.

From "Cybersecurity Analysis" (b) (4)

Section 4 – System Architecture
4.1 – Assets
4.2 – Components

(b) (4)

**Reviewer Comment:**

**The software/cybersecurity consultant as well as the lead consultant reviewer found the information adequate to satisfy the Agency's request. The cybersecurity documentation provided by the Sponsor adequately addressed the system architecture, risks, risk mitigations, vulnerabilities, and testing commensurate with the FDA's Guidance for management of cybersecurity in medical devices.**

2. You have provided a summary of your validation and verification plan within (b) (4) and (b) (4). However, no detailed test cases, including test protocol, pass/fail criteria, test data and results were provided. Please update both (b) (4) and (b) (4) with the requested information.

**Sponsor Response:**
(b) (4) have updated both (b) (4) and (b) (4) with new versions of the Verification & Validation Matrix. The updated documents *"Verification and Validation Matrix myBetaApp"* (b) (4) *) and "Verification and Validation Matrix Navigator"* (b) (4) *are located* in (b) (4) and in (b) (4) ( (b) (4) , respectively).

These two documents have been changed to provide additional information in line with the Agency's request. The following updates have been made to both documents:

| Column name | Type of change | Description of update |
|---|---|---|
| Protocol | Updated information | Additional information has been added, to provide a more direct guidance for the reader to the test protocol reference, where applicable. |
| Test parameter | New column | This column presents, where applicable, direct references to test cases (and a short description of the test case) applied to verify or validate a specific requirement. In usability validation the term Task is used instead of Test case. |
| Test method | New column | This column gives the reference to the document where it describes how to perform the test case. |
| Acceptance criteria | New column | This column describes the criteria for acceptance of a result from executing the test cases referred in the column Test parameter. Detailed pass/fail criteria are found in the documents referred in the column Test method. |
| Report and test data | Updated title of column and added information | Where applicable a direct reference has been added to the document where test data is found. |

| Column name | Type of change | Description of update |
|---|---|---|
| Test result | New column | This column provides a summary statement regarding the outcome of the performed validation or verification testing. |

**Reviewer Comment:**
**The software consultant found the Sponsor's response adequate. The [redacted] and [redacted] were updated with the verification and validation testing information recommended by the software Guidance document. The lead reviewer did not find the information to be fully adequate due to the outstanding documentation for a Moderate Level of Concern Software – please see Section XI.**

3. Please provide the release version and release date of MyBETAapp and BETACONNECT Navigator within their respective [redacted] files.

**Sponsor Response:**
In response to your information request [redacted] has added the release descriptions of the master version of myBETAapp and BETACONNECT Navigator to the [redacted] and [redacted] see the document "Software Release Description myBETAapp and Navigator" [redacted] located in [redacted], respectively.

These master versions have been developed according to the [redacted]. The products have successfully passed the validation and verification activities and are ready for the final localization confirmation upon approval in the US. The localization procedure is described in the [redacted] Overview document (section 7.1)

**Reviewer Comment:**
**The software consultant and lead consultant reviewer found the Sponsor's response to be adequate. The version history was successfully updated.**

## IX. Information Requests Sent on 10/06/2016

1. Provide a comparability protocol to establish how future post-approval changes to the combination product will be addressed within the application. Be sure to detail the type of post-approval changes, supporting information including any analysis and risk assessment activities, a plan to implement the change(s), and, if appropriate, a proposed reduced reporting category for the change(s).

**Sponsor Response:**
In line with recent FDA guidance1 recognizing that "unnecessary submission of post-approval supplements to FDA for changes that could be managed solely by a manufacturer's PQS" could have a negative impact on change management activities and could discourage continual improvement", Bayer's Post Approval submission strategy seeks to maximize the use of [redacted] Bayer's Quality Systems, in particular [redacted]

The Sponsor provided a Comparability Protocol with the following format:

| Proposed Comparability Protocol to qualify software changes to myBETAapp |
| --- |
| (b) (4) |

**Reviewer Comment:**
**The consultant reviewer found the comparability protocol deficient in that it did not reference the Sponsor's (b) (4) components that may require a submission. See Section X for more details.**

## X. Information Requests Sent on 01/24/2017

1. While changes within the Navigator software's current functionality may not require a submission, you should include a statement within the current comparability protocol that changes to the Navigator software functionality may require a submission. The submission type should be determined based on the criteria in 21 CFR 314.50. Alternatively, you may (b) (4) state that an updated comparability protocol to address potential changes to the Navigator software functionality would be submitted in a prior approval supplement and approved in advance of implementing any such changes.

**Sponsor Response:**
Bayer agrees that the descriptions in the current comparability protocol primarily refer to the (b) (4). We agree to provide an updated comparability protocol to address (b) (4) r, and a statement has been added to the comparability protocol indicating this. In the interim, prior to the approval of a (b) (4) if any changes are necessary, they will be assessed and submitted according to the existing regulations and guidance documents.

The Sponsor submitted Version 2 of the Comparability Protocol with the following added:

"A (b) (4) at a later date via a Prior Approval Supplement for the (b) (4) ."

**Reviewer Comments:**
**The Sponsor's update to the comparability protocol is adequate.**

2. Your proposed comparability protocol includes a statement about the (b) (4) software. FDA does not agree that the two bulleted items are inclusive of the established conditions for the software. As described in the draft guidance you reference ("Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products"), established conditions assure the quality of an approved product and must be reported if changed. Therefore, the established

conditions for this software would include those aspects of the software that, if changed, you would report to FDA in a PAS, CBE, or annual report. However, because the referenced guidance is in draft and has not yet been implemented, and since a list of established conditions is not necessary to support approval of the comparability protocol, we suggest that you revise the protocol to remove references to established conditions.

**Sponsor Response:**
Bayer agrees, and has provided an updated comparability protocol with all references to [redacted] removed.

**Reviewer Comments:**
**The Sponsor's update to the comparability protocol is adequate.**

## XI. Information Request – Sent on 05/16/17

1. Within [redacted] and [redacted] you list the software [redacted] the Premarket Software Guidance, and the [redacted] and supply the documentation as recommended by the Software Premarket Guidance to [redacted]. [redacted] and [redacted] should both [redacted] as well as any other software documentation necessary to support the Moderate level of concern if not already included.

**Sponsor's Response:**

Our assignment of a [redacted] with the software (myBETAapp or Navigator) [redacted] However based on the FDA's request [redacted]. For convenience we will be providing the following documents as part of this response:

1. Risk analysis of [redacted]
2. Risk Management Report – There were [redacted]

Please note, that another [redacted]

Additional documents requested by the Software Premarket Guidance will also be provided to the FDA by Bayer via email, [redacted]. We expect to provide the following documents by the end of business on Friday, May 19.

1. Architecture Design Chart - Architecture and interface specifications
2. Software Design Specification
   a. [redacted] myBETAapp [redacted]
   b. [redacted]
   c. [redacted]

The following documents can be provided by Monday, May 22.

1. Software development environment description of the myBETAapp and Navigator. This documentation consists of a summary of the software development environment, the configuration management as well as a detailed report on the software maintenance plan.
   a. Development Environment Description
   b. Software Maintenance Plan

[redacted] believes that the remaining requirements are covered by documents already provided in the [redacted]

**Reviewer Comments:**

- **The Sponsor updated the [redacted] myBETAapp and Navigator software [redacted] as requested by the Agency.**
- **The [redacted] for both the myBETAapp and Navigator along with an associated risk analysis. Review of this information resulted in no unacceptable risk associated with the [redacted]**
- **The Architecture Design Chart, Software Design Specification, and Software Development Environment Description documents were added to [redacted] and [redacted] as stated and are acceptable to the lead reviewer.**

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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.**

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/s/

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REBECCA N LOPEZ
05/25/2017

**HUMAN FACTORS RESULTS 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:** | May 16, 2017 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | BLA 103471/S-5189 |
| **Product Name and Strength:** | myBETAapp Mobile and Desktop Application |
| **Product Type:** | Combination Product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Bayer |
| **Submission Date:** | March 10, 2017; April 7, 2017; April 28, 2017 |
| **OSE RCM #:** | 2016-1769-1 |
| **DMEPA Primary Reviewer:** | Ebony Whaley, PharmD, BCPPS |
| **DMEPA Team Leader:** | Lolita White, PharmD |
| **DMEPA Associate Director for Human Factors:** | QuynhNhu Nguyen, MS |
| **DMEPA Deputy Director:** | Irene Z. Chan, PharmD, BCPS |

## 1 REASON FOR REVIEW

The Division of Neurology Products (DNP) requested that we review Bayer's Response to the Agency's Information Request and the revisions to the URRA, myBETAapp Instructions for Use (IFU), Betaconnect Autoinjector IFU, and comparability protocol for Betaseron (BLA 103471/S-5189). The revisions are in response to recommendations that we made in an Information Request[a] stemming from our previous human factors (HF) validation study results review.[b]

## 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 | N/A |
| Human Factors—Use-Related Risk Analysis | C |
| ISMP Newsletters | N/A |
| FDA Adverse Event Reporting System (FAERS)* | N/A |
| Other-Comparability Protocol and Response to Information Requests | F |
| 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

### 3.1 HUMAN FACTORS VALIDATION STUDY METHODOLOGY FOR MYBETAAPP MOBILE APPLICATION AND DESKTOP APPLICATION

In our March 15, 2017 review of the myBETAapp HF validation study results, we noted (b) (4) two use scenarios related to the myBETAapp email reminder, which could result in extra dose medication errors. Those use scenarios are:

[a] Information Request for Betaseron BLA 103471/S-5189. Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of New Drugs, Division of Neurology Products (US); 2017 MAR 10; 2017 FEB 24.
[b] Whaley, E. Human Factors Results Review for Betaseron myBETAapp (BLA 103471/S-5189). 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); 2017 MAR 15. 23 p. OSE RCM No.: 2016-1769.

1. [redacted] evaluate the use scenario where the participant is required to respond to the myBETAapp email reminder feature.
2. [redacted] evaluate the scenario where the participant opts to [redacted] and how a user would respond to receiving [redacted].

[redacted] We identified concerns with the availability of two different alarm/messaging features, which might contradict the injection data and needed clarification regarding how these features are triggered. [redacted]

[redacted]. Bayer also states that the clinical harm associated with unintentional administration of an extra dose is low and submitted a literature reference (BEYOND study) to support this claim.[c]

[redacted]

[c] O'Connor P, Filippi M, Arnason B, et al. 250 µg or 500 µg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. *Lancet Neurology.* 2009;8:889-897.

(b) (4)

Generally, DMEPA's goal is to prevent medication errors from happening before they occur. With the proposed mitigation of (b) (4) Thus, at this time, we agree that no further human factors assessment of the myBETAapp email reminder use scenarios is needed, and Bayer may proceed with implementing this additional feature if they choose to. We also consulted the clinical review team, who agreed with Bayer's conclusion that the clinical harm associated with unintentional administration of a one-time extra dose is low.

In our review of the myBETAapp HF validation study summary of results, we also identified that (b) (4) we asked that Bayer provide further information on the outcome of the failure. The HF validation study report stated that the participant failed the task and did not recover from the error; however, further details were not provided and it was unclear whether the participant successfully completed subsequent use tasks. Bayer provided additional details surrounding the failure, and we find Bayer's response sufficient and do not recommendation further revisions or mitigations in response to this participant failure with Task 1.

### 3.2 MYBETAAPP APP SAMPLE PRODUCT REVIEW

In our review of the myBETAapp app, we previously identified several concerns and discrepancies with the sample versions of myBETAapp mobile application and desktop application. Specifically, we identified a lack of clarity of terminology for technical support, unclear warning messages during pairing of the AI, discrepancies in the screenshots and actual screens of the app, (b) (4)

[redacted](b) (4). We recommended that Bayer revise myBETAapp to mitigate the identified issues for risk of medication error.

### 3.3 MYBETAAPP INSTRUCTIONS FOR USE (IFU) AND BETACONNECT AUTOINJECTOR INSTRUCTIONS FOR USE (IFU)

In our review of the myBETAapp app, we previously identified areas of needed improvement within the myBETAapp IFU and Betaconnect AI IFU which stem from the HF data submitted by the Sponsor and are also based on postmarket lessons learned from other similar drug products. Bayer revised the myBETAapp IFU and Betaconnect AI IFU and we find the revisions acceptable.

### 3.4 COMPARABILITY PROTOCOL

In a February 24, 2017 IR, we requested that Bayer revise the proposed myBETAapp Comparability Protocol. We recommended that Bayer:

1. Perform a use-related risk analysis (URRA) for each proposed change to the user interface to determine the impact on the safe and effective use of myBETAapp.
2. Revise the comparability protocol to indicate that if a change to the user interface will not negatively impact the safe and effective use of the user interface, it may be submitted in the Annual Report.
3. Revise the comparability protocol to indicate that if a change to the user interface may impact the safe and effective use of the product, it should be submitted to the Agency for review as a Prior Approval Supplement (PAS) or Changes Being Effected (CBE) supplement.

In response to our recommendations, Bayer provided further clarifications and justifications for the statements in the comparability protocol.

Bayer agreed to perform a URRA for each potential change to user interface. However, Bayer did not agree that each URRA should be submitted to the Agency for review prior to implementation of the change. Bayer stated that doing so "will likely result in a large number of submissions and an undue burden on both the FDA and Bayer".

We reviewed Bayer's response to our recommendations and we agree that Bayer does not need to submit a URRA for every proposed change to the user interface. A risk based paradigm should be applied when determining whether a change to the user interface should be submitted to the Agency. [redacted](b) (4)

[redacted] (b) (4) [redacted]. We identified several areas of the comparability protocol that should be addressed. We provide recommendations for these areas of the concern in section 4.1.

## 4 CONCLUSION & RECOMMENDATIONS

We conclude that the revised myBETAapp app, revised myBETAapp IFU, and revised Betaconnect AI IFU are acceptable. However, our review of the comparability protocol identified areas that warrant revision.

### 4.1 RECOMMENDATIONS FOR BAYER

We reviewed your submitted IR responses and find the revised myBETAapp app, revised myBETAapp IFU, and revised Betaconnect AI IFU acceptable at this time, and no additional human factors testing is required. We acknowledge [redacted] (b) (4) [redacted] and determine that you may proceed with implementing this additional feature if you choose to. However, our review identified areas of concern with your comparability protocol that require additional modifications at this time. Please address the following:

A. Comparability Protocol

1. We agree with your request not to submit every use-related risk analysis (URRA) for Agency review. A risk based paradigm should be applied when determining whether a change to the user interface may warrant additional data and should be submitted to the Agency. We expect you will evaluate any change to the user interface, including the IFU, and conduct an updated URRA to determine whether the change can negatively impact the safe and effective use of your product. If changes to the user interface are determined to have substantial potential to negatively impact safe and effective use of the product (e.g., introduce new risks) or are intended to address a known use error identified in the postmarket setting, then those changes should submitted as a prior approval supplement (PAS). If changes are determined to have moderate potential to negatively impact safe and effective of the product, then those changes should be submitted as a changes being effected in 30 days (CBE-30) supplement. If the changes do not negatively impact safe and effective use of the product then they can be submitted in the annual report.

2. In the Type of Change category [redacted] (b) (4) we recommend that the examples are revised to reflect changes to the user interface that will not introduce increased or new risks.
3. In the Type of Change category [redacted] (b) (4) we recommend that the examples are revised to reflect changes to the user interface that will not introduce increased or new risks.
4. In the Type of Change category "[redacted] (b) (4) As such, we recommend that the description is revised to reflect changes to the user interface that will not negatively impact safe and effective of the product.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Betaseron that Bayer submitted on July 29, 2016.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Betaseron</th></tr>
<tr><td>Initial Approval Date</td><td>July 23, 1993</td></tr>
<tr><td>Active Ingredient</td><td>interferon beta-1b</td></tr>
<tr><td>Indication</td><td>Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>(b) (4)</td></tr>
<tr><td>Strength</td><td>0.3 mg</td></tr>
<tr><td>Dose and Frequency</td><td>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>
<tr><td colspan="4">Table 1: Schedule for Dose Titration</td></tr>
<tr><td></td><td>BETASERON Dose*</td><td>Percentage of recommended dose</td><td>Volume</td></tr>
<tr><td>Weeks 1-2</td><td>0.0625 mg</td><td>25%</td><td>0.25 mL</td></tr>
<tr><td>Weeks 3-4</td><td>0.125 mg</td><td>50%</td><td>0.5 mL</td></tr>
<tr><td>Weeks 5-6</td><td>0.1875 mg</td><td>75%</td><td>0.75 mL</td></tr>
<tr><td>Week 7 and thereafter</td><td>0.25 mg</td><td>100%</td><td>1 mL</td></tr>
<tr><td colspan="4">* Dosed every other day, subcutaneously</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>- A single-use vial containing 0.3 mg BETASERON<br>- A PFS containing 1.2 mL diluent (Sodium Chloride, 0.54% solution)<br>- A vial adapter with a 30-gauge needle attached<br>- 2 alcohol prep pads<br>- The optional BETACONNECT autoinjector is not supplied with BETASERON, but is available for patients with a prescription for BETASERON</td></tr>
<tr><td>Storage</td><td>Store BETASERON vials at room temperature 68°F to 77°F (20°C to 25°C).</td></tr>
</table>

## APPENDIX C. HUMAN FACTORS—UPDATED myBETAapp USE-RELATED RISK ANALYSIS

| User Tasks | Discussion | Use Error | Consequence | Priority |
|---|---|---|---|---|
| **Injection Recording and review** | | | | |
| Patient records injection either manually or by synchronizing the autoinjector to myBETAapp | After each injection, user has the options of manually recording his injection or synchronizing with the autoinjector for automated transmission. | Patient does not manually record injection or synchronize with the autoinjector | Injection history not complete in myBETAapp. No direct impact on injection or therapy | Low |
| Patient records injection site in myBETAapp | After each injection, user has the option of manually recording his injection site in myBETAapp in case of a manually recorded injection and in case of synchronizing an injection from the autoinjector, the user has the option to confirm the suggested injection site or to select the correct injection site. | Patient does not record injection site | myBETAapp will continue to suggest the injection site from the last recorded injection. User may inject into the same site twice | Low |
| Patient reviews his own patient injection log in myBETAapp | Patient review his recorded injection history at any time after his first recorded injection | Patient does not review | No direct impact on injection or therapy | Low |
| **Added URRA lines from November 16, 2016 response** | | | | |
| Patient receives a Recording Reminder | Patient receives an e-mail reminding them to record an injection taken | Patient does not review email, or reviews e-mail and does not record injection | No direct impact on injection or therapy. If patient does not record their manual injection, or synced with the BETACONNECT, and they have not done so before, information in log less helpful to patient and caregiver | Low |
| | | Patient reviews e-mail and records injection, but injection not taken | No direct impact on injection or therapy. The patient is provided a prescription and other reminders to inject. Recordings an injection that was not taken only impacts the accuracy of the log and makes the information in log less helpful to patient and caregiver | Low |
| Patient does not receive a Recording Reminder | Patient does not choose to receive an e-mail reminding him to record an injection taken | Not use error. Patient has not chosen to receive reminders | No direct impact on injection or therapy | None |

| Added URRA lines for March 10, 2017 response | | |
|---|---|---|
| (b) (4) | No direct impact on therapy. If patient does take a second dose of 250 mcg of Betaseron, risk of adverse effects is low. Conclusion is supported by the BEYOND clinical trial demonstrating comparable safety profile of double the approved dose (O'Connor, et al, Lancet Neurol 2009; 8: 889–97) | Low |
| | No direct impact on injection or therapy. Patient has received a single dose of medication | None |

## APPENDIX F. OTHER SOURCES USED FOR THIS REVIEW

1. Sponsor's Response to the Agency's February 24, 2017 Information Request
    a. Submitted on March 10, 2017
2. Sponsor's Response to the Agency's March 21, 2017 Information Request
    a. Submitted on April 7, 2017
3. Revised myBETAapp Comparability Protocol
    a. Submitted on March 10, 2017

## 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,[d] along with postmarket medication error data, we reviewed the following myBETAapp and Betaconnect Autoinjector labels and labeling submitted by Bayer on April 7, 2017 and April 28, 2017.

- myBETAapp Instructions for Use (not pictured)
- Betaconnect Autoinjector Instructions for Use (not pictured)

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

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EBONY A WHALEY
05/16/2017

LOLITA G WHITE
05/16/2017

QUYNHNHU T NGUYEN
05/16/2017

IRENE Z CHAN
05/17/2017

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

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

# Memorandum

**Date:** May 15, 2017

**To:** Billy Dunn, MD, Director
Division of Neurology Products (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, DNP

Rebecca N. Lopez, Regulatory Project Manager, DNP

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

**Through:** Mathilda Fienkeng, PharmD, RAC, Team Leader, OPDP

**Subject:** **BLA 103471, S-5189**
OPDP labeling comments for BETASERON (interferon beta-1b) for injection, for subcutaneous use

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In response to DNP's consult request dated September 22, 2016, OPDP has reviewed the proposed Instructions for Use (IFU) for "myBETAapp" and for the Betaconnect autoinjector. This supplemental application (S5189) proposes the optional use of the "myBETAapp" and "BETACONNECT Navigator" software applications. The "myBETAapp" is a software application for computers and mobile devices for patients to track and record their injections; and the "BETACONNECT Navigator" is web-based software for healthcare providers to access and review a patient's injection information that were recorded and uploaded to the database by patients through the "myBETAapp."

OPDP has conducted a high level review of the "myBETAapp" and the Betaconnect autoinjector IFUs received from DNP (Rebecca N. Lopez) via electronic mail on May 9, 2017, and has no comments at this time. Please note that OPDP's review of these materials was limited to content pertaining to the drug product, and we defer to CDRH for the review of non-drug related content.

If you have questions, please contact Aline Moukhtara at (301) 796-2841 or Aline.Moukhtara@fda.hhs.gov. OPDP appreciates the opportunity to provide comments.

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ALINE M MOUKHTARA
05/15/2017

**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: | May 10, 2017 |
| To: | William Dunn, MD<br>Director<br>**Division of Neurology Products (DNP)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Marcia Williams, PhD<br>Team Leader, Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Sharon W. Williams, MSN, BSN, RN<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| Subject: | Review of Patient Labeling: Instructions for Use (IFU) |
| Drug Name (established name): | BETASERON (interferon beta-1b) |
| Dosage Form and Route: | injection, for subcutaneous use |
| Application Type/Number: | BLA 103471 |
| Supplement Number: | 5189 |
| Applicant: | Bayer HealthCare Pharmaceuticals, Inc. |

## 1 INTRODUCTION

On July 29, 2016, Bayer HealthCare Pharmaceuticals submitted for the Agency's review a Prior Approval Supplement (PAS) for the myBETAapp and BETACONNECT Navigator. On April 27, 2017, the Applicant submitted an amendment to the PAS which incorporated the Division of Medication Error Prevention, and Analysis (DMEPA) recommendations into the submitted IFUs. The purpose of the submission is to seek approval for both software applications, which are separate but interconnected. myBETAapp is a stand-alone software application for computers and mobile devices that allows patients to track and record their own injections. The BETACONNECT Navigator is web-based software used by healthcare providers to access and review a patient's injection information, that were recorded and uploaded to the database by patients through the myBETAapp. BETASERON (interferon beta-1b) injection, for subcutaneous use is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Neurology Products (DNP) on Septermber 22, 2016, for DMPP to review the Applicant's proposed Instructions for Use (IFU) for BETASERON (interferon beta-1b) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the BETACONNECT autoinjector, myBETAapp, and BETACONNECT Navigator IFUs was completed on March 15, 2017.

DMPP conferred with DMEPA and deferred to DMEPA and the Center for Devices and Radiologic Health (CDRH) to provide review comments for the myBETAapp and BETACONNECT Navigator Instructions for Use.

## 2 MATERIAL REVIEWED

- Draft BETASERON (interferon beta-1b) injection, for subcutaneous use BETACONNECT IFU received on April 27, 2017, and received by DMPP on May 9, 2017.
- Draft BETASERON (interferon beta-1b) injection, for subcutaneous use Prescribing Information (PI) received on April 27, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on May 9, 2017.

## 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.

In our review of the IFU we:

- simplified wording and clarified concepts where possible
- removed unnecessary or redundant information
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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SHARON W WILLIAMS
05/10/2017

MARCIA B WILLIAMS
05/10/2017

**HUMAN FACTORS RESULTS 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:** | March 15, 2017 |
| **Requesting Office or Division:** | Division of Neurology Products (DNP) |
| **Application Type and Number:** | BLA 103471/S-5189 |
| **Product Name and Strength:** | myBETAapp Mobile and Desktop Application |
| **Product Type:** | Combination Product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | Bayer |
| **Submission Date:** | July 29, 2016 |
| **OSE RCM #:** | 2016-1769 |
| **DMEPA Primary Reviewer:** | Ebony Whaley, PharmD, BCPPS |
| **DMEPA Team Leader:** | Lolita White, PharmD |
| **DMEPA Associate Director for Human Factors:** | QuynhNhu Nguyen, MS |
| **DMEPA Deputy Director:** | Irene Z. Chan, PharmD, BCPS |

## 1 REASON FOR REVIEW

On July 29, 2016, Bayer submitted a prior approval supplement (S-5189) to introduce the myBETAapp mobile medical application and desktop application to function as an injection tracking and recording tool for patients with relapsing forms of multiple sclerosis (MS) who are prescribed Betaseron. Bayer also proposes to introduce the Betaconnect Navigator system, an internet browser-based product intended to allow healthcare providers to access and review patient's injection data obtained from myBETAapp.

The Division of Neurology Products (DNP) consulted DMEPA to review the proposed labeling for myBETAapp and the Betaconnect Autoinjector, as well as the human factors (HF) validation study results for myBETAapp and Betaconnect Navigator.

### 1.1 PRODUCT INFORMATION AND BACKGROUND

The myBETAapp mobile application and desktop application (collectively referred to as 'app' or 'myBETAapp') and the Betaconnect Navigator internet-based application can be used optionally by patients and caregivers who use Betaseron (see Appendix A). The myBETAapp mobile application and desktop application records injection data, including dose and injection site, and suggests injection sites to users to encourage injection site rotation. Users can manually enter injection data into the applications if they are using either prefilled syringes or the Bayer Betaconnect Autoinjector (AI). Alternatively, the Betaconnect AI can connect to either application so that locally stored injection information can be transmitted to the applications (via Bluetooth or USB connection), bypassing the need for manual entry. We note the injection site suggestion feature of the myBETAapp app provides recommendations that may influence or alter user behavior (i.e. promotes use of injection site rotation).

MyBETAapp will be available as an Android and IOS mobile application and as a Windows and (b) (4) desktop application. Bayer indicated there are two differences between the mobile application and desktop application: (1) In the desktop application, the navigation menu is always visible, but in the mobile application the menu is hidden until the menu icon in the top left corner is tapped, and (2) in the desktop application, the Betaconnect AI is connected via an USB cable to the computer (b) (4) and for the mobile application a wireless Bluetooth connection should be established. We also note that use of myBETAapp mobile application on a mobile phone (b) (4) as compared to use of myBETAapp desktop application on a computer. The differences between the mobile application and desktop application were included as part of the myBETAapp HF validation studies. Additionally, according to Bayer there are (b) (4)

Betaconnect Navigator is an internet-based software application that collects therapy adherence data and provides secure internet-based platforms for HCPs and patients to record and share information on aspects of treatment. At this time, we have determined that Betaconnect Navigator does not provide clinical decision support features and functionality that are expected to require alteration of HCP, patient, or caregiver behavior. Thus, we focus our HF evaluation in this review on the HF validation study results for the myBETAapp mobile application and desktop application utilized by patients and caregivers as they will interact with the app and take appropriate action in response to alerts and instructions.

### 1.2 REGULATORY HISTORY

Betaseron (interferon beta-1b) was approved on July 23, 1993 and is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The Betaconnect Autoinjector (AI) is an optional device that can be used to administer Betaseron and was approved under BLA 103471/Supplement-5186 on September 25, 2015. The Betaconnect AI is not supplied with Betaseron and is prescribed separately. Bayer did not previously submit the HF validation study protocols for the myBETAapp mobile application and desktop application or Betaconnect Navigator for Agency review prior to Bayer initiating the studies.

## 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 | N/A |
| FDA Adverse Event Reporting System (FAERS)* | N/A |
| Other-Information Requests | F |
| 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

### 3.1 HUMAN FACTORS VALIDATION STUDY METHODOLOGY FOR MYBETAAPP MOBILE APPLICATION AND DESKTOP APPLICATION

Two HF validation studies were conducted for the myBETAapp mobile application and desktop application. The first HF validation study was conducted with 30 untrained participants representative of the intended user population (patients with multiple sclerosis [MS]). Based on failures occurring with Task 2: *Launch and configure software application* and subjective feedback collected in the first HF validation study, Bayer implemented mitigations to change the user interface of the launch and configuration of the app (e.g. Task 2). Therefore, the second HF validation study was limited in scope to evaluate the changes to the user interface that impact Task 2: *Launch and configure software application*. The second validation study was performed with 15 untrained participants, representative of the intended user population (see Appendix C). Therefore, 45 unique participants were evaluated between the two HF validation studies.

We reviewed Bayer's identified use tasks, use related risk analysis, study protocol and methodology and we identified two use scenarios not considered in the use related risk analysis for the safe use of this product. As such, these use tasks were not evaluated by the Sponsor in their HF validation studies.

1. The validation study does not evaluate the use scenario where the participant is required to respond to the email reminder feature of myBETAapp. The email reminder feature is part of the myBETAapp mobile application and desktop application, and it is intended to remind patients to [redacted (b) (4)] However, we have concerns that such a reminder could be misinterpreted by end users as a [redacted (b) (4)]. The Sponsor has not provided sufficient data to evaluate how users' will respond to this email reminder feature.

2. The validation study does not evaluate the scenario where the participant opts to [redacted (b) (4)] The Betaconnect AI reminder is an audible alarm on the AI itself that will sound every 48 hours, and it is intended to remind the patient to inject their dose. As noted above, the email reminder is part of the myBETAapp mobile and desktop applications and is [redacted (b) (4)]. We

are concerned that [redacted] (b) (4) The Sponsor has not provided data to evaluate how users' will respond to this scenario.

At this time, we do not have any data to support how representative users respond to the reminder features as described above. Additionally, we do not have any information on the clinical impact of task failures associated with the tasks outlined above. Thus, we find this to be a deficiency within the study.

### 3.2 HUMAN FACTORS VALIDATION STUDY RESULTS FOR MYBETAAPP MOBILE APPLICATION AND DESKTOP APPLICATION

We evaluated the results of both HF validation studies. Of the 30 participants in the first HF validation study, there were a total of 5 task failures. As previously noted, the second HF validation study focused only on Task 2. Of the 15 participants in the second HF validation study, there were 3 task failures. We discuss below the failures during the performance of the following four use tasks:

Task 1: Install the software, Log in, and Assign autoinjector if appropriate (Failures: n=2)

The first HF validation study identified 2 failures that occurred with assigning an autoinjector. Assigning an autoinjector is a task that is applicable if an end user administers their medication with a Betaconnect AI as opposed to a prefilled syringe. With a Betaconnect AI, the user can either manually enter their injection data (referred to as "manual injection data logging") or they can pair the device with the mobile medical application via Bluetooth or use a USB cable to connect to the desktop application(referred to as "automatic injection data logging"). Assigning the autoinjector allows the user to automatically transmit the injection data that is locally stored on the Betaconnect AI to myBETAapp.

- 1 participant assigned to the desktop application arm with manual injection data logging selected "Yes" when the app prompted them to determine whether they would be using the Betaconnect AI. However, the participant did not have a Betaconnect AI. The sponsor's root cause analysis (RCA) determined that when entering their user settings, the participant overlooked the portion of the prompt regarding use of Betaconnect AI and believed they were confirming that set-up of the app was complete. The HF validation study report stated that the participant did not recover from the error; however, further details were not provided, and we were unclear if the participant did complete the injection. This information is

needed from the Sponsor to understand the downstream effects of not correctly choosing the product presentation.

- 1 participant assigned to the mobile application arm with automatic injection data logging failed to assign the Betaconnect AI to myBETAapp. The sponsor's RCA determined that the participant overlooked the instruction to "Turn on your autoinjector" and attempted to tap the Betaconnect AI to pair the device without turning the device on. The participant also noted having difficulty identifying the serial number on the Betaconnect AI and stated that they "never saw the [serial] number".

We reviewed this task using the sample app provided by the Sponsor. Because the sample app has pre-defined user settings, we were not able to fully assess the registration process.

Bayer did not propose mitigations in response to the failures that occurred with this task and determined the risks associated with the task are low with no patient safety-related harm anticipated. Both the app and the myBETAapp IFU instruct users to turn the Betaconnect AI on before attempting to the pair the device, and we determined these instructions are adequately prominent. We note that difficulty or failure with this task may prevent users from being able to pair their Betaconnect AI to myBETAapp, but this would not inhibit patients from performing an injection when necessary or entering their data manually. We agree with the Sponsor's assessment of the risk associated with these failures. However, we note that during the HF study, participant feedback indicated difficulty locating the serial number. We note that in Section 5 Connecting Betaconnect Autoinjector to myBETAapp of the myBETAapp IFU there are graphics that indicate the location of the serial number on the Betaconnect Autoinjector and the graphics may be small and difficult to visualize. Based on this submitted data, we recommend further improvements to the graphics to enable users to locate the serial number on the Betaconnect AI. We provide our recommendations in Section 7.1 below.

Task 2: Launch and configure software application (Failures: n=3)

The second HF validation study identified 3 failures that occurred with configuring and customizing injection site rotation. Within the myBETAapp mobile application and desktop application, users have the ability to specify which injection sites they want to exclude (e.g., some users may prefer not to inject in the right arm, and in that case the application would not include that administration site in the rotation if the user appropriately deselects all of the right arm sub-sites: upper, mid, low). To complete this task in the HF validation study, participants were instructed to set a specific last injection date and were also instructed to exclude the front right thigh injection site as a preferred injection site for their injection site rotation.

- 1 participant did not correctly set the last injection site. The sponsor's RCA indicated that the participant believed that the injection site selection process involved opening the pop-up window for an injection site and clicking 'done'. The sponsor's RCA also noted that the participant did not understand that each injection sub-site needed to be individually selected within the pop-up window to trigger injection site de-selection. The participant was selecting entire injection area by "tapping on the circles," which initially opens up a pop up window. Once the pop up window appeared, the participant clicked "Done" and believed she had selected all three of the sub-sites that appeared within the pop up window. By ignoring the "front right thigh" in her selection process, she was including it in her injection site rotation. She did not realize that she needed to individually tap the dots next to each listed sub-site in the pop up window and turn them white in order to deselect them.

  Bayer indicated in their analysis that that the participant "had the wrong interaction model". This may have been due to the participants confusion by instructions that had been given in the task card (part of the study, not part of the user interface) or the participant may have misinterpreted or ignored the printed text instructions located above the body diagram within the application, which read "If you do not typically inject in certain areas, you may exclude them from the rotation schedule. Tap the circles to select or deselect a site…" The sponsor attributes this task failure to study artifact. We agree with the sponsor's assessment, though this suggests that the underlying design of the study materials was inadequate.

- 1 participant did not correctly set the last injection date. The sponsor's RCA indicated that the participant believed they needed to select a specific date to correspond with each injection site. This assumption caused the participant to change the date that they had previously correctly set for last injection date (per the task card). The sponsor attributed the failure to the participant misunderstanding the task card for this specific feature of myBETAapp (which the sponsor refers to as "wrong interaction model") and the sponsor did not provide additional detail regarding why the participant misunderstood this task. We agree with the sponsor's assessment that the participant misunderstood the task card, though again this suggests that the underlying design of the study materials was inadequate.

- 1 participant did not correctly set the last injection site. The participant reported that they misread the last injection site information on the task card ("I misread abdomen") and thus, entered the incorrect last injection site. The sponsor determined this failure can be attributed to study artifact. We agree with the sponsor's assessment, though again this suggests that the underlying design of the study materials was inadequate.

Bayer did not propose further mitigations because they determined that the risks associated with Task 2 were low with no patient safety-related harm anticipated. The available remaining data suggests that the mitigations put in place to address the failures previous seen with Task 2 in the first HF validation study were adequate.

We note that difficulty or failure with this task may affect the selection of preferred injection sites (i.e. non-preferred injection sites are recommended). However, we agree with the Sponsor that these task failures would not result in patient harm. The applications only suggest injection sites. The user may choose to use an alternative injection site if desired (i.e. right thigh is suggested but patient prefers not inject in the thigh and chooses the abdomen instead). We find the residual risk acceptable.

We also note that difficulty or failure to correctly set the last injection date during the app set-up and registration process may affect the injection schedule; however this scenario may result in a one-time incorrect date of administration error. However, after the first error, subsequent doses will default to an every other day frequency of administration and the schedule will be corrected. We find the residual risk acceptable.

Task 5: Log injection data from mock injection in software application

Failure (n=2)

The first HF validation study identified 1 failure that occurred with logging injection data in myBETAapp.

- One participant assigned to the desktop application arm with automatic injection data logging did not unplug the Betaconnect AI from the computer after assigning the AI to myBETAapp. If the AI is left connected by USB to computer, the AI will not inject. The sponsor's RCA indicated that the participant attempted to administer a mock injection; however, due to the Betaconnect AI being connected to the computer, the Betaconnect AI would not operate. The participant stated that if at home, they would give the injection manually and contact their nurse. After intervention from the study moderator, the participant unplugged the Betaconnect AI, successfully performed the mock injection and transferred the injection data to the app. The sponsor did not provide additional detail regarding why the participant misunderstood this task.
- One participant assigned to the mobile arm with automatic injection data logging experienced a failure in which the injection data from the Betaconnect AI did not automatically transfer (i.e. automatic injection data logging). The sponsor's RCA indicated that this failure occurred due to a previous error with Task 1 in which the

participant did not successfully pair the device. Because the error occurred with Task 1 and the device was not paired with myBETAapp, the participant was unable to complete the automatic injection data logging. The participant stated that the data was not importing and chose to log the injection data manually instead. The sponsor determined that this outcome was a task failure. However, we note that although the participant did not complete the automatic data transfer, the participant successfully completed the task in an appropriate manner by logging the injection data manually. Therefore, we would not have characterized this as a task failure.

Bayer did not propose mitigations in response to the above failures and determined the risks associated with the task to be low with no patient safety-related harm anticipated. We note that difficulty or failure with this task may prevent users from manually entering or automatically transferring documentation of injection data into myBETAapp; however, difficulty or failure in documenting a dose within myBETAapp would not inhibit patients from performing an injection when necessary. Thus, we find the residual risk acceptable.

We also note that difficulty or failure to unplug the Betaconnect AI prior to attempting to administer Betaseron may result in dose omission or delay of therapy. We determined that this risk can be further mitigated.

In the section "Connecting BETACONNECT Autoinjector to myBETAapp" of the myBETAapp IFU, users are informed on how to register their Betaconnect AI to the app (i.e. pair the device). For users who access myBETAapp via a computer, the myBETAapp IFU informs user that they will not be able to perform injections while the Betaconnect AI is connected to a USB port and also instructs users to connect the Betaconnect AI to the computer after performing an injection. We also note that myBETAapp includes the statement "(b) (4) [redacted]. We provide our recommendations in Section 7.1 below.

Task 6: Confirm or record the actual injection site used (Failures: n=1)

The first HF validation study identified one failure that occurred with logging the injection site in myBETAapp.

- One participant assigned to the mobile arm with automatic injection logging experienced a failure in which the incorrect injection site was recorded. The participant was prompted to inject the front left thigh (per the task card) and

verbally confirmed the instruction. However, the participant performed the mock injection on the front right thigh instead. The participant did not edit the injection site field, which was pre-populated with the intended injection site (left thigh) from the task card. The participant realized that they made a mistake but did not attempt to correct it because they believed it was not within the scope of the task.

Bayer determined the risks associated with the task to be low with no patient safety-related harm anticipated. We disagree with Bayer's conclusion that there is no risk for harm. We note that difficulty or failure with this task may result in myBETAapp applications suggesting an injection site that was recently injected. As a result, patients may have an increased likelihood of injection site reactions if the same injection site is used consecutively. However, in this instance, we note that the participant recognized that the injection site was incorrect and the failure to record the actual injection site used occurred due to the participant's misunderstanding of the scope of the HF validation study; therefore, we attribute this failure to study artifact. We find the residual risk acceptable.

## 4 MYBETAAPP APP SAMPLE PRODUCT REVIEW

Bayer provided Android tablet devices, Android mobile phones, and iPhones loaded with the myBETAapp mobile app for our review of the myBETAapp mobile device platform and provided website access for review of the computer platform.

We reviewed the myBETAapp mobile application and desktop application in the iOS and Android operating systems and also in the desktop platform. During our independent review of myBETAapp mobile application and desktop application sample, we identified the following areas of needed clarification within myBETAapp.

1. We note that the title of the tab directing users for technical support is called (b) (4). It may not be clear to users that are searching for technical support information within the app to look within this tab. This terminology can be revised to decrease confusion should technical support be needed. Though this was not identified in the HF study, we note that there was no specific task included in the study related to obtaining technical support information, which may explain the lack of HF data collected by the Bayer in this space.
2. We identified a potentially confusing message when unpairing the Betaconnect AI from myBETAapp. The message states that users may unpair the device; however, it also states that pairing is permanently bound. This inconsistency may cause confusion for users who are attempting to unpair the Betaconnect AI from the application. Though this was not identified in the HF study, we note that there was no specific task included in the study related to unpairing a Betaconnect AI device, which may explain the lack of HF data collected by Bayer in this space.

3. There is a discrepancy between the screenshots of myBETAapp provided by Bayer in response to the Agency's November 10, 2016 IR and the screen displays of the sample version of myBETAapp. To clarify the registration process, Bayer provided a screenshot of the app which included the text "Enter your MixJect code contained in your BETASERON single dose box". We note that this text may help to inform users of the location of the code necessary to complete the registration process; however, this text does not appear in the sample versions of myBETAapp provided to the Agency. This discrepancy should be resolved to mitigate the risk of confusion with the registration process.

In addition to the areas identified above, upon our independent use of the sample applications, we noted that there is additional functionality in the app that was not specifically tested in the HF validation studies nor mentioned in the MyBETAapp Instructions for Use (IFU). This additional functionality is as follows:


We are concerned that having the functionality without including instructions for users on how to accomplish these tasks may lead to confusion for some users. While we would not consider these to be critical tasks, we recommend that appropriate instructions are included in the MyBETAapp IFU.

## 5 MYBETAAPP INSTRUCTIONS FOR USE (IFU)

Our review of the proposed myBETAapp IFU identified the following areas of needed improvement that should be addressed to decrease the risk of medication error. Some of these recommendations stem from the HF data submitted by the Sponsor and some recommendations are based on postmarket lessons learned from other drug products:

1. The figures within Section 5 Connecting Betaconnect Autoinjector to myBETAapp of the IFU can be improved upon to enable users to clearly determine the location of the serial number on the Betaconnect AI. Difficulty or failure with this step may prevent users from being to pair their Betaconnect AI to myBETAapp. We note that this concern was identified as subjective feedback within Task 1 of the HF study.

2. There is a discrepancy between the myBETAapp IFU and the myBETAapp app in Section 5 Connecting Betaconnect Autoinjector to myBETAapp. In the myBETAapp IFU, users are instructed to (b) (4). However, we note that the sample versions of myBETAapp provided to the Agency do not include the tab or screen (b) (4). This discrepancy may lead to difficulty or failure with pairing the Betaconnect AI to myBETAapp. We note that this discrepancy did not lead to failure in the HF study; however, we recommend this inconsistency is corrected prior to approval of this supplement.

The myBETAapp IFU is available electronically within the mobile application and desktop application. While electronic labeling is allowable, we considered whether this could potentiate the risk for error if patients are unable to simultaneously utilize the app and refer to the instructions. However, upon further evaluation we discovered that the myBETAapp IFU will also be available online (via the desktop version of the app) and can be printed by patients and caregivers if necessary. Thus, this provides an alternate mechanism for users to access the IFU in the event that they wish to follow along with the IFU rather than rely on recall of instructions previously read. We find this approach appropriate.

## 6 BETACONNECT AUTOINJECTOR INSTRUCTIONS FOR USE (IFU)

In section 3.2 of this review, we discussed the Task 5 failure where a participant attempted to administer an injection while the Betaconnect AI was connected to the computer by USB. We noted that the Betaconnect AI IFU (b) (4) therefore, we recommend that the Betaconnect AI IFU is revised to include a message similar to what is displayed in myBETAapp.

## 7 CONCLUSION & RECOMMENDATIONS

We have determined that there are data deficiencies in the human factors results report. In particular, we identified tasks related to reminder functionality of the app that were not evaluated in the study. Therefore, at this time we cannot conclude that the proposed MyBETAapp user interface supports the safe and effective use of Betaseron. Additional information will be needed from the Sponsor.

Based on the available data from the HF validation studies and our independent review of the sample applications, myBETAapp IFU and the Betaconnect AI IFU, we have determined that additional changes to the user interface are needed to minimize the risk for medication error and to provide clarity. We advise our proposed recommendations are implemented prior to approval of this supplement, and these can be implemented without requiring additional human factors testing.

### 7.1 RECOMMENDATIONS FOR BAYER

Please address the following based on your submission of Human Factors (HF) validation study results, myBETAapp samples and associated instructions for use.

A. MyBETAapp Human Factors Validation Study Methodology
    1. We identified data deficiencies in your human factors results report which may lead to unintentional administration or extra dose errors. In particular, we identified two use scenarios related to reminder functionality of the app that were not evaluated in the study (e.g. the use scenario where the participant is required to respond to the email reminder feature of myBETAapp and the scenario where the participant opts to (b) (4) Therefore, at this time we cannot conclude that the proposed MyBETAapp user interface supports the safe and effective use of Betaseron. We ask that you provide additional information, as described in the Agency's February 24, 2017 Information Request.

B. MyBETAapp Mobile and Desktop App Sample Product Review:
    Our review of the MyBETAapp App samples identified the follow areas of concerns:
    1. The terminology used within the information menu of the myBETAapp lacks clarity when directing users for technical support. The title of the support tab within the information menu tab is called (b) (4). This section of the information tab is intended to direct users to Technical Support information; however the use of this terminology (b) (4) may contribute to confusion. The tab for technical help should be titled in lay terms.
    2. When registering and pairing Betaconnect AI to myBETAapp, users receive a message which lacks clarity and may lead to confusion. The message states (b) (4) Betaconnect binds it permanently to your myBETAapp account and (b) (4). Do you want to (b) (4) this Betaconnect?" However, we note that myBETAapp does allow users to unpair the Betaconnect AI and if done, users receive the message (b) (4) remove the Betaconnect from this list?" This inconsistency may confuse users who are attempting to unpair the Betaconnect AI from the application. Therefore, we recommend you clarify the language used in this statement and also better define the task. (i.e. describe the functionality or feature that (b) (4)
    3. We identified a discrepancy between the screenshot of myBETAapp provided by Bayer in response to the Agency's November 10, 2016 IR and the screen display within the sample version of myBETAapp provided to the Agency. Your IR

provided a screenshot of registration process that depicts the step in which users input a code from Betaseron into myBETAapp. The screenshot of the app you submitted includes the text (b) (4) MixJect (b) (4) This discrepancy between the sample app and the screenshots submitted should be resolved to ensure consistency and to ensure that users are given explicit instructions on how to locate the code that is necessary to complete the myBETAapp registration process. Additionally, ensure that any revisions are applied to applicable graphics within the myBETAapp IFU.

4. We note that the app (b) (4) . We recommend that you revise the IFU to include this information (i.e. under Troubleshooting) as it is possible that the patient (b) (4)
5. We note that the app (b) (4) We are concerned this may lead to confusion. We recommend you revise the IFU to include this information (i.e. under Troubleshooting). We recommend this revision to mitigate the risk of administration and inappropriate frequency of administration errors.

C. MyBETAapp App Instructions for Use (IFU)

Our review of the MyBETAapp App IFU identified some areas of concerns that require additional modifications. Please address the following:

1. The figures within Section 5 Connecting Betaconnect Autoinjector to myBETAapp can be improved upon. The subjective feedback from participants in your HF validation study suggests that the serial number on the Betaconnect Autoinjector may be difficult to identify. We note that the figures in Section 5 Connecting Betaconnect Autoinjector to myBETAapp are (b) (4) . As such, we recommend that the figures are (b) (4) to enable users to clearly locate the serial number on the Betaconnect AI. Difficulty or failure with this step may prevent users from being able to pair their Betaconnect AI to myBETAapp.

2. There is a discrepancy between the myBETAapp IFU and the myBETAapp app in Section 5 Connecting Betaconnect Autoinjector to myBETAapp, which may lead to confusion. In the IFU Section 5 Connecting Betaconnect Autoinjector to myBETAapp, users are instructed to (b) (4) . However, in the myBETAapp mobile application and desktop application, the menu does not include the tab or screen (b) (4) and instead includes the tab (b) (4). This inconsistency may lead to difficulty or failure with pairing the Betaconnect AI to myBETAapp. We recommend the terminology is consistent to mitigate the risk of confusion regarding pairing the device.

D. Betaconnect Autoinjector IFU

Our review of the Autoinjector identified one area of concern that should be addressed:

1. We note that the (b) (4) We are concerned that difficulty or failure to complete this task will result in dose omission or delay in therapy. We recommend that the labeling is revised to include a warning message similar to what is displayed in myBETAapp to decrease risk of error of dose omission or delay of therapy.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Betaseron that Bayer submitted on July 29, 2016.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Betaseron</th></tr>
<tr><td>Initial Approval Date</td><td>July 23, 1993</td></tr>
<tr><td>Active Ingredient</td><td>interferon beta-1b</td></tr>
<tr><td>Indication</td><td>Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>(b) (4)</td></tr>
<tr><td>Strength</td><td>0.3 mg</td></tr>
<tr><td>Dose and Frequency</td><td>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>
<tr><td colspan="4">Table 1: Schedule for Dose Titration</td></tr>
<tr><td></td><td>BETASERON Dose*</td><td>Percentage of recommended dose</td><td>Volume</td></tr>
<tr><td>Weeks 1-2</td><td>0.0625 mg</td><td>25%</td><td>0.25 mL</td></tr>
<tr><td>Weeks 3-4</td><td>0.125 mg</td><td>50%</td><td>0.5 mL</td></tr>
<tr><td>Weeks 5-6</td><td>0.1875 mg</td><td>75%</td><td>0.75 mL</td></tr>
<tr><td>Week 7 and thereafter</td><td>0.25 mg</td><td>100%</td><td>1 mL</td></tr>
<tr><td colspan="4">* Dosed every other day, subcutaneously</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>- A single-use vial containing 0.3 mg BETASERON<br>- A PFS containing 1.2 mL diluent (Sodium Chloride, 0.54% solution)<br>- A vial adapter with a 30-gauge needle attached<br>- 2 alcohol prep pads<br>- The optional BETACONNECT autoinjector is not supplied with BETASERON, but is available for patients with a prescription for BETASERON</td></tr>
<tr><td>Storage</td><td>Store BETASERON vials at room temperature 68°F to 77°F (20°C to 25°C).</td></tr>
</table>

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## APPENDIX B. PREVIOUS DMEPA REVIEWS

### B.1 Methods

On October 18, 2016, we searched the L:drive and AIMS using the term, Betaseron, to identify reviews previously performed by DMEPA.

### B.2 Results

Our search identified two previous reviews[a,b] pertinent to this review, and we confirmed that our previous recommendations were implemented.

[a] Harris, J. Human Factors and Label and Labeling Review for Betaseron BLA 103471/S-5186. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 AUG 31. RCM No.: 2014-2537.

[b] Harris, J. Human Factors and Label and Labeling Review for Betaseron BLA 103471/S-5186. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 SEP 24. RCM No.: 2014-2537-1.

## APPENDIX C. SUMMARY OF THE HUMAN FACTORS VALIDATION STUDY

| | |
|---|---|
| **Combination product description:** | myBETAapp mobile and desktop application |
| **Intended users** | Patients with multiple sclerosis (MS) who have been prescribed Betaseron are the primary intended users of the myBETAapp. Patients may be assisted by a non-professional caregiver. |
| **Intended use** | To help patients and their healthcare providers (HCP) monitor treatment. MyBETAapp is intended to assist patients in recording and tracking their drug injections and injection sites, without providing specific treatment or treatment suggestions. Also, for patients who allow third party access to their historical data via cloud-based sharing, myBETAapp enables viewing of these data by the HCP and receiving from the HCP pre-defined in-app messages regarding their adherence to dosing. |
| **Intended use environment** | Home |
| **Study objective** | To evaluate that the intended users of myBETAapp can safely and effectively perform tasks for the intended uses in the expected use environments. Additionally, a second validation study was performed following the initial HF validation study to validate Task 2 of the study. |
| **Method** | Observation and Simulated Use; Observation of tasks performed to demonstrate successful use of the myBETAapp to record injections using the device and accompanying labels, labeling and instructions for use (IFU). |
| **Study Group #1** | 30 MS patients who were currently on or had recently taken injectable medication(s) for their MS. Patients were not trained prior to HF validation testing.<br>- 7 Mobile application arm + manual data entry<br>- 7 Mobile application arm+ automatic data transfer<br>- 9 Desktop application arm + manual data entry<br>- 7 Desktop application arm + automatic data transfer |
| **Study Group #2 (Task 2 Validation)** | 15 MS patients<br>- 7 Mobile application arm<br>- 8 Desktop application arm |
| **Training** | Patients using myBETAapp will be provided a short description of the app and its purpose, but will have no formal training prior to using it. The Instructions for Use (IFU) as a guide is embedded in the app and the device user interface consists of a number of screens guiding the user through the different functions of the app. Patients will also have |

<table>
<tr><td></td><td>access to nurse support and will have an available help-desk to call for technical support.</td></tr>
<tr><td>Tasks</td><td>1. Installation of the software<br>2. Launch and configuration of software application (validated in 2nd HF study)<br>3. Pairing with Autoinjector<br>4. Review of injection schedule<br>5. Review of injection site<br>6. After injection, Log-in of a manual injection OR<br>7. Connect the autoinjector with the computer or mobile device<br>8. Manually record the injection site used in the software application<br>9. Review messages from HCP (if authorized)</td></tr>
<tr><td>HF validation study Results</td><td>
<table>
<tr><th>Task</th><th>Task Success Criteria</th><th>Success Rate on Task</th></tr>
<tr><td rowspan="6">1</td><td>OVERALL RESULTS: TASK 1<br>Install the software [Desktop Arm only] and, if appropriate, assign an autoinjector</td><td>93% (28 of 30)</td></tr>
<tr><td>[Desktop Arm] Install the software</td><td>100% (15 of 15)</td></tr>
<tr><td>Log into the application</td><td>100% (30 of 30)</td></tr>
<tr><td>[Automatic] Assign autoinjector to the account</td><td>93% (14 of 15)</td></tr>
<tr><td>[Manual] Respond NO to using a BETACONNECT autoinjector OR recover is YES if selected</td><td>93% (14 of 15)</td></tr>
<tr><td rowspan="4">2</td><td>OVERALL RESULTS: TASK 2<br>Launch and configure software application</td><td>53% (16 of 30)</td></tr>
<tr><td>Set last injection date according to information provided on the Injection (task) Card</td><td>97% (29 of 30)</td></tr>
<tr><td>Set last injection site according to information provided on the Injection (task) Card</td><td>97% (29 of 30)</td></tr>
<tr><td>Set injection site suggestions according to information provided on the Injection (task) Card</td><td>53% (16 of 30)</td></tr>
<tr><td>3</td><td>OVERALL RESULTS: TASK 3<br>Check if an injection is scheduled for today</td><td>100% (30 of 30)</td></tr>
<tr><td>4</td><td>OVERALL RESULTS: TASK 4<br>Find the injection site for today's injection</td><td>100% (30 of 30)</td></tr>
</table>
<table>
<tr><th>Task</th><th>Task Success Criteria</th><th>Success Rate on Task</th></tr>
<tr><td rowspan="4">5</td><td>OVERALL RESULTS: TASK 5<br>Log injection data in the software application</td><td>93% (28 of 30)</td></tr>
<tr><td>[Manual] Record a manual injection</td><td>100% (15 of 15)</td></tr>
<tr><td>[Mobile Arm/ Automatic] Bluetooth enabled and mobile device turned on prior to injection</td><td>87% (7 of 8)</td></tr>
<tr><td>[Desktop Arm/ Automatic] Connect autoinjector and PC with USB cable after injection</td><td>86% (6 of 7)</td></tr>
<tr><td>6</td><td>OVERALL RESULTS: TASK 6<br>Log the actual injection site used</td><td>97% (29 of 30)</td></tr>
</table>
</td></tr>
</table>

| | |
|---|---|
| **HF validation study Results (Task 2 only)** | |

| Task Success Criteria | Success Rate on Task | |
|---|---|---|
| **OVERALL RESULTS:** Launch and configure software application | 80% (12 of 15) | |
| **RESULTS ON TASK 2 SUB-CRITERIA** | | |
| Select "Yes" to already started injections? | 100% (15 of 15) | |
| Set last injection date according to information provided on the Injection (task) Card | 93% (14 of 15) | |
| Set last injection site according to information provided on the Injection (task) Card | 87% (13 of 15) | |
| Select "Yes" to customize your injection sites? | 100% (15 of 15) | |
| Set injection site suggestion according to information provided on the Injection (task) Card | 100% (15 of 15) | |
| Activate "Continue" button | 100% (15 of 15) | |

## APPENDIX F. OTHER SOURCES USED FOR THIS REVIEW—SPONSOR RESPONSE TO INFORMATION REQUESTS

To better inform our review, an Information Request (IR) was sent to the sponsor on September 28, 2016 to request several clarifications regarding myBETAapp and Betaconnect Navigator including a comprehensive use-related risk analysis, the human factors validation study protocol, and a comparison of the computer and mobile device versions of myBETAapp. In the October 13, 2016 reply, Bayer did not adequately address all the agency's questions.

On November 10, 2016, we sent a second IR to request revisions to the use-related risk analysis for myBETAapp to include scenarios regarding the injection reminder feature within myBETAapp. We also requested participant demographics, success and failure criteria for each tasks, study methods, and root cause analysis data for specific reported failures with the MyBETAapp mobile app (see Appendix C). In their November 18, 2016 response, the sponsor submitted a revised URRA, detail regarding study methods and patient demographics, and a detailed description of all failures noted in the HF validation studies.

Response to FDA Info Request Dated 28Sep2

response-to-informati on-request-dated-10n

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## 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,[c] along with postmarket medication error data, we reviewed the following myBETAapp and Betaconnect Autoinjector labels and labeling submitted by Bayer on July 29, 2016.

- myBETAapp Instructions for Use (not pictured)
- Betaconnect Autoinjector Instructions for Use (not pictured)

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

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/s/

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EBONY A WHALEY
03/15/2017

LOLITA G WHITE
03/15/2017

QUYNHNHU T NGUYEN
03/15/2017

DANIELLE M HARRIS on behalf of IRENE Z CHAN
03/16/2017

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# BLA 103471/S-5189

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

## Lopez, Nahleen (FDA)

**From:** Vicenty, Francisco
**Sent:** Friday, May 26, 2017 11:50 AM
**To:** Bastings, Eric
**Cc:** Ware, Jacqueline H; Lopez, Nahleen (FDA); Marler, John; Boam, Ashley; Kamon-Brancazio, Jamie; Gilbert, Susannah
**Subject:** RE: BLA 103471/5189

Thank you for the additional information and clarity.

I am forwarding the Susannah Gilbert the email for an official response. We understand the details better now and agree with the proposal. Susannah will be able to provide an official response to this discussion. Will an email be sufficient or do you require a signed off memo?

**Cisco Vicenty**
**Program Manager – Case for Quality (Acting)**

**CDRH**
**Office of Compliance**
**U.S. Food and Drug Administration**
**Tel: 301-796-5577**
**Francisco.vicenty@fda.hhs.gov**

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**********

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
**https://www.research.net/s/cdrhcustomerservice?O=300&D=360&B=365&E=&S=E**

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**From:** Bastings, Eric
**Sent:** Friday, May 26, 2017 10:49 AM
**To:** Vicenty, Francisco
**Cc:** Ware, Jacqueline H; Lopez, Nahleen (FDA); Marler, John; Boam, Ashley
**Subject:** BLA 103471/5189

Cisco,

BLA 103471 is for Betaseron, a licensed biologic for the treatment of MS. The product can be administered using au autoinjector named Betaconnect, which has been reviewed by CDRH prior to its approval a few years ago.

Supplement 5189 was submitted by the sponsor in support of a smartphone application (myBETAapp) and desktop software system (Betaconnect Navigator) for use with the Betaconnect autoinjector.

The supplement does not include any change to the Betaconnect autoinjector, and only includes software applications and related labeling changes.

We have determined that the supplement poses no more than minimal risk to patients, and approval is recommended by all review disciplines.

We believe that inspection of the device manufacturing site is not necessary before we issue our approval letter (goal date is today), and can be deferred to post-approval of the supplement. Do you concur?

Thanks.

Eric

Eric Bastings

Deputy Director,

Division of Neurology Products, OND/CDER

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/s/

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REBECCA N LOPEZ
05/26/2017

## Lopez, Nahleen (FDA)

**From:** Marler, John
**Sent:** Monday, May 15, 2017 8:47 PM
**To:** Lopez, Nahleen (FDA)
**Cc:** Rodichok, Lawrence
**Subject:** FW: Betaseron BLA 103471/S-5189

Please place in the record to document Dr. Rodichok's review of the sponsor's data to support the safety of a double dose of Betaseron (b) (4) unintentional second injection.

John

---

**From:** Rodichok, Lawrence
**Sent:** Wednesday, April 12, 2017 3:12 PM
**To:** Whaley, Ebony
**Cc:** White, Lolita
**Subject:** RE: Betaseron BLA 103471/S-5189

Assuming that this would not be a recurring event for an individual patient then I agree that the journal report supports the safety of a single 500 microgram dose, i.e. mistakenly taking two 250 microgram doses in a 24 hour period.

---

**From:** Whaley, Ebony
**Sent:** Wednesday, April 12, 2017 2:38 PM
**To:** Rodichok, Lawrence
**Cc:** White, Lolita
**Subject:** Betaseron BLA 103471/S-5189

Hello,

I am the DMEPA review for Betaseron (BLA 103471) Supplement 5189 for the myBETAapp mobile medical application and I am currently reviewing the sponsor's response to questions we submitted to them regarding the myBETAapp email reminder feature.

In our human factors review, we noted that myBETAapp includes an optional email reminder feature that is intended to remind users to record their injection data in myBETAapp and that the currently marketed Betaconnect Autoinjector has an injection reminder feature (b) (4) unintentionally administer two doses of Betaseron. We asked the Sponsor to assess the use risk and any harm that may occur.

The sponsor provided supporting data to demonstrate that the risk associated with (b) (4) The sponsor also noted that in the event at extra dose is unintentionally administered, the risk of harm is low and provided a supporting study (BEYOND study).

From a DMEPA position, we are fine with their assessment and justification. However, we would appreciate your input regarding the Sponsor's assessment of severity of clinical harm associated with an unintentional administration of an extra dose of Betaseron. I have attached the study that the sponsor referenced for your review.

Thanks,

Ebony
240.402.3325

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/s/

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REBECCA N LOPEZ
05/16/2017

LAWRENCE D RODICHOK
05/16/2017

JOHN R MARLER
05/16/2017

## Lopez, Nahleen (FDA)

**From:** Kelley, Laurie
**Sent:** Tuesday, March 21, 2017 8:57 AM
**To:** Resmi John
**Cc:** Lopez, Nahleen (FDA)
**Subject:** Betaseron BLA 103471/S-5189
**Attachments:** BLA 103471 Human Factors Recommendation.docx

John

The attached document contains DMEPA's comments and recommendations regarding BLA 103471 and the Human Factors (HF) validation study results, myBETAapp samples as well as the associated Instructions For Use. Please confirm receipt.

Regards,
Laurie

Laurie Kelley, PA-C
Regulatory Project Manager
FDA, CDER
Office of New Drugs/Division of Neurology Products
Bldg. 22, Room 4200
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Please address the following based on your submission of Human Factors (HF) validation studyresults, myBETAapp samples and associated instructions for use.

A. MyBETAapp Human Factors Validation Study Methodology

1. We identified data deficiencies in your human factors results report which may lead to unintentional administration or extra dose errors. In particular, we identified two use scenarios related to reminder functionality of the app that were not evaluated in the study (e.g. the use scenario where the participant is required to respond to the email reminder feature of myBETAapp and the scenario (b) (4) Therefore, at this time we cannot conclude that the proposed MyBETAapp user interface supports the safe and effective use of Betaseron. We ask that you provide additional information, as described in the Agency's February 24, 2017 Information Request.

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[redacted] This discrepancy between the sample app and the screenshots submitted should be resolved to ensure consistency and to ensure that users are given explicit instructions on how to locate the code that is necessary to complete the myBETAapp registration process. Additionally, ensure that any revisions are applied to applicable graphics within the myBETAapp IFU.

4. We note that the app [redacted]
We recommend that you revise the IFU to include this information (i.e. under Troubleshooting) as it is possible that the patient [redacted]

5. We note that the app [redacted]
We are concerned this may lead to confusion. We recommend you revise the IFU to include this information (i.e. under Troubleshooting). We recommend this revision to mitigate the risk of administration and inappropriate frequency of administration errors.

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device.

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/s/

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REBECCA N LOPEZ
05/08/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103471/S-5189

**ACKNOWLEDGMENT --**
**PRIOR APPROVAL SUPPLEMENT**
**FILING COMMUNICATION –**
**NO FILING REVIEW ISSUES IDENTIFIED**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Resmi John, MD
Associate Director, Global Regulatory Affairs
100 Bayer Blvd., P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. John:

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

| | |
|---|---|
| **BLA NUMBER:** | 103471 |
| **SUPPLEMENT NUMBER** | 5189 |
| **PRODUCT NAME:** | Betaseron (interferon beta 1-b) lyophilized powder for subcutaneous inj 0.3mg/vial |
| **DATE OF SUBMISSION:** | July 29, 2016 |
| **DATE OF RECEIPT:** | July 29, 2016 |

This supplemental application proposes the optional use of the "myBETAapp" and "BETACONNECT Navigator" software applications.

We also refer to your amendments dated September 16, 2016, and September 29, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 29, 2017. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V.[1]

[1] http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170 htm

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings such as the filing, planning, mid-cycle, team, and wrap-up meetings. Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues such as the submission of amendments. We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 1, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

In addition, we request that you submit the following information:

> Provide a comparability protocol to establish how future post-approval changes to the combination product, particularly for the software application, will be addressed within the application. Be sure to detail the type of post-approval changes, supporting information including any analysis and risk assessment activities, a plan to implement the changes, and, if appropriate, a proposed reduced reporting category for the changes. Please provide this protocol by November 14, 2016.

## FDAAA TITLE VIII RESPONSIBILITIES

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).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **BLA 103471/S-5189**submitted on July 29, 2016, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

**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.

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI),and Instrutions for Use. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
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 ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient labeling, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, call LCDR Nahleen Lopez, Regulatory Project Manager, at (240) 402-2659.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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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.**

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/s/

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ERIC P BASTINGS
10/11/2016