CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103780Orig1s5196

Trade Name:	REBIF
Generic or Proper Name:	Interferon beta-1a
Sponsor:	EMD Seron, Inc.
Approval Date:	September 27, 2016
Indication:	REFIB is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.

CENTER FOR DRUG EVALUATION AND RESEARCH

103780Orig1s5196

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103780Orig1s5196

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103780/S-5196

SUPPLEMENT APPROVAL
PLLR WAIVER DENIED
PLLR EXTENSION GRANTED

EMD Serono, Inc.
Attention: Lisa M. Hyde
Associate Director, Global Regulatory Medical Devices & Diagnostics
Global Regulatory Affairs & Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Hyde:

Please refer to your Supplemental Biologics License Application (sBLA), dated November 26, 2015, received November 27, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Rebif (interferon beta-1a) Injection.

This Prior Approval supplemental biologics application provides for the addition of a 2D barcode and near field communication (NFC) tag to the labeling of the Rebif Rebidose autoinjector, and for the use of the MSdialog System, which permits electronic documentation of medication injections when using the Rebif Rebidose autoinjector.

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 and with the minor editorial revisions listed below.

- MSdialog Mobile Application Instructions for Use (IFU): revise page 29, which is currently blank to state:

  CAUTION:
  Please be aware that recorded injections cannot be deleted.
  For assistance, you may contact your doctor or:
  MS LifeLines at
  1-877-447-3243

We also note and refer to your commitment to revise the MSdialog Mobile Application IFU, as described in our September 21, 2016, electronic communication, and as discussed with Drs. Marler, Ware and Lopez on September 27, 2016.

We based our review of the MSdialog Web Apps and their associated IFUs on our assessment of the low potential risk to patients posed by the Apps' features and functionality. You are advised that future modifications to the MSdialog Web Apps may require a regulatory submission and a more in-depth Agency review depending on what the modifications are. In determining the appropriate regulatory submission (if any) 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.

PLLR WAIVER REQUEST

We also refer to your submission dated July 22, 2016, requesting a waiver, under 21 CFR 201.58, of the requirements on content and format of labeling described at 21 CFR 201.56 and 201.57. Specifically, you are requesting a waiver of the Pregnancy and Lactation Labeling Rule (PLLR) requirements for this supplement.

We have reviewed your request and have determined that a waiver is not justified. However, we are granting an extension of the date for compliance with the labeling requirements until June 30, 2018, or with submission of another efficacy supplement, whichever is sooner.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that 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 November 27, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 103789/S-5196**" Approval of this submission by FDA is not required before the labeling is used.

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

PROMOTIONAL MATERIALS

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

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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

REPORTING REQUIREMENTS

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

If you have any questions, call 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:
Content of Labeling

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

/s/

ERIC P BASTINGS
09/27/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103780Orig1s5196

LABELING

***Rebif*® *Rebidose*®**

Instructions For Use

Exclusively for use with

***Rebif*®**
(interferon beta-1a)
subcutaneous injection

Welcome

This guide contains information on how to use Rebif® Rebidose®, a pre-assembled, single-use autoinjector that administers one dose of Rebif® (interferon beta-1a) for the treatment of relapsing forms of multiple sclerosis.

See the Full Prescribing Information for information about Rebif, including risks associated with the drug such as suicide and depression, hepatic injury, and injection site reactions.

Please read these instructions carefully before you start using the Rebif® Rebidose® and remember, you must have received the appropriate training before injecting.

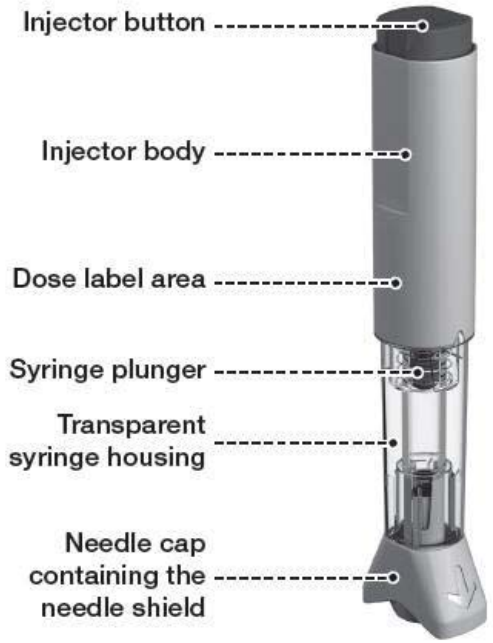
If at any time, you have questions or concerns, please contact your health care provider or call MS LifeLines at 1-877-447-3243.

Rx Only

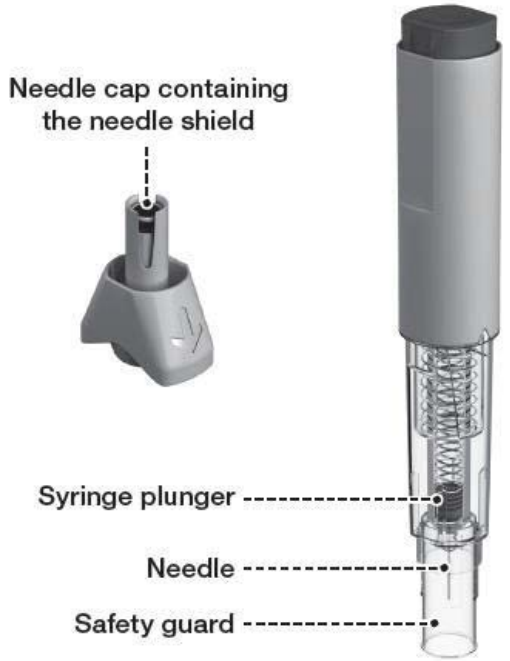
Contents

Rebif® Rebidose® features

Before injection:



After injection:



⚠ Warnings

- Always use the injection technique advised by your health care provider and contact them with any questions you might have.
- Always keep the Rebif® Rebidose® autoinjector out of the reach of children.
- **Do not** share your autoinjector with anyone. Doing so may result in injury, including the transmission of infectious blood-borne diseases. Adhere to strict safety and antiseptic precautions at all times.
  - **Do not** insert your fingers into the opening of the safety guard.
  - **Do not** try to re-use a Rebif® Rebidose® autoinjector that has already been used.
  - Adhere to proper disposal procedures to avoid a needle stick injury.

⚠ Warnings

- Check the expiration date on the Rebif® Rebidose® autoinjector label and its carton. If the medication has expired, **Do not** use it.
- Examine the contents of the syringe carefully through the transparent housing. The liquid should be clear or slightly yellow. Inspect for cracks or breakage in the syringe or other parts. **Do not** use Rebidose® if it is cracked or broken or if the liquid is cloudy, discolored or contains particles.
- If the Rebidose® has been dropped more than 3 feet, or if it looks damaged for any reason, **Do not** use it. Instead, dispose of it in an acceptable biohazard (sharps) container and use a new Rebidose® autoinjector.
- Contact your health care provider about any damaged Rebif® Rebidose® autoinjector.

Important Information

- Store your Rebif® Rebidose® autoinjectors in a refrigerator until ready for use.

- If you or someone around you is injured by the needle, contact your health care provider immediately and dispose of the Rebif® Rebidose® autoinjector in an acceptable biohazard (sharps) container.

- Injecting Rebif® the medicine using the Rebidose® autoinjector may cause skin reactions including soreness, redness, pain, bruising, or swelling. Tell your health care provider about any skin reactions that become swollen, painful, or look infected and do not heal within a few days.

- Use a different site each time you inject. **Do not** inject Rebif® where your skin is irritated, reddened, bruised, infected or abnormal in any way.

- The Rebif® Rebidose® autoinjector contains a glass syringe. In very rare cases, the syringe may break during the injection. If this happens, immediately dispose of any broken glass and the damaged Rebidose® autoinjector in the biohazard (sharps) container, taking necessary precautions to avoid injury. Contact your health care provider or MS LifeLines at 1-877-447-3243 immediately.

How Supplied

Rebif® Rebidose® is available in 3 dose sizes.
Check that the dose of Rebif® is the one prescribed for you by looking at the Rebidose® carton and at the dose label on the Rebidose® autoinjector.

Rebif® Rebidose® autoinjectors are supplied in these 3 packaging presentations:

- Titration Pack
    - 6 Rebif® 8.8 mcg Rebidose® autoinjectors with a lime green injector button.
    - 6 Rebif® 22 mcg Rebidose® autoinjectors with a yellow injector button.
- 12 Rebif® 22 mcg Rebidose® autoinjectors with a yellow injector button.
- 12 Rebif® 44 mcg Rebidose® autoinjectors with a teal green injector button.

Titration

At the beginning of Rebif® treatment, your health care provider may prescribe a titration phase to gradually increase to the intended dosage.

The Rebif® Rebidose® Titration Pack contains six 8.8 mcg autoinjectors with a lime green injector button and six 22 mcg autoinjectors with a yellow injector button.

The titration period lasts 4 weeks and during this time, you will administer 12 injections:

- **Weeks 1 and 2:** Use one 8.8 mcg autoinjector three times a week, at least 48 hours apart.
- **Weeks 3 and 4:** Use one 22 mcg autoinjector three times a week, at least 48 hours apart.

Your health care provider may provide a different dose and schedule.

Recording your injections

You may find it helpful to record information about your 3 weekly injections to discuss with your health care provider.

You can record your injections:

- By hand, using a tracking sheet (see page 14)
- By scan, using the MSdialog Mobile App that can see or scan information from your autoinjector's label (see page 15)

Contact your health care provider or MS LifeLines at 1-877-447-3243 for information about recording options.

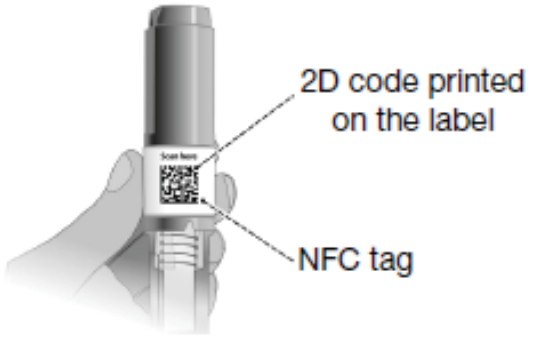
Use tracking sheet

Week 1	Inj. Site	Date & Time	Site Reaction	
Inj. 1			Yes	No
Inj. 2			Yes	No
Inj. 3			Yes	No
Week 2	**Inj. Site**	**Date & Time**	**Site Reaction**	
Inj. 1			Yes	No
Inj. 2			Yes	No
Inj. 3			Yes	No
Week 3	**Inj. Site**	**Date & Time**	**Site Reaction**	
Inj. 1			Yes	No
Inj. 2			Yes	No
Inj. 3			Yes	No
Week 4	**Inj. Site**	**Date & Time**	**Site Reaction**	
Inj. 1			Yes	No
Inj. 2			Yes	No
Inj. 3			Yes	No

Use MSdialog Mobile App

If you have an Apple iPhone® or Google Android™ smartphone, you can use the MSdialog Mobile App to record your injections.

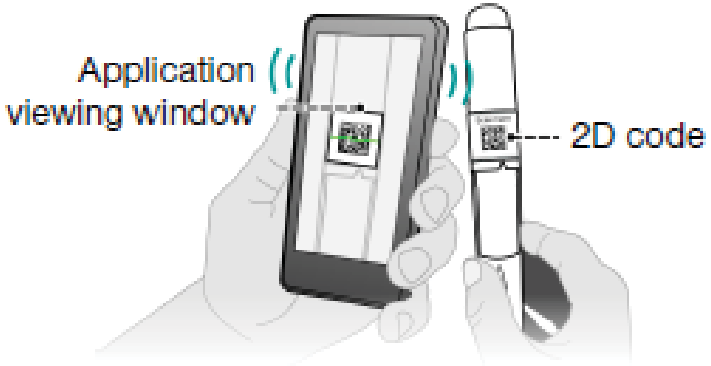
The Rebif® Rebidose® autoinjector label features a **2D code** and a **Near-Field Communication (NFC) tag**. The MSdialog Mobile App can scan the code or tag to record information about the autoinjector.



Apple and iPhone are trademarks of Apple Inc. and Google and Android are trademarks of Google Inc.

Choose one of the following two options:

Option 1: Scan 2D code



1) Point the smartphone's camera at the autoinjector's label, centering the 2D code in the application's viewing window.

2) Hold the smartphone steady until it makes a sound or vibrates, indicating that the 2D code has been scanned.

Option 2: Read NFC tag

1) Hold the NFC tag against the back of the smartphone, making sure the label contacts the smartphone's back.

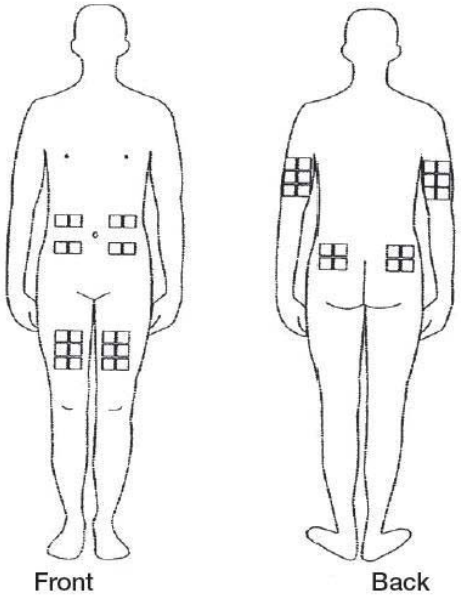
2) Hold the smartphone steady until it makes a sound or vibrates, indicating that the NFC tag has been read.

Choosing an injection site

The best sites for giving a subcutaneous injection are those areas with a layer of fat between the skin and muscle. These include the thigh, the outer surface of the upper arm, the stomach and the buttocks.

Do not use the area near your waistline or within 2 inches of your navel.

Only choose one site for injection. Use a different site each time you inject.



⚠ Caution

Do not inject Rebif® where your skin is irritated, reddened, bruised, infected or abnormal in any way.

Step 1: Prepare for your injection

1.1) Before you begin, you may find injecting more comfortable if you allow time for the Rebif® to warm up to room temperature before injecting. Therefore, it is recommended that you remove the Rebif® Rebidose® autoinjector from the refrigerator at least 30 minutes prior to use.

⚠ Caution

Do not heat or microwave a Rebidose® autoinjector.

1.2) Put all of the items listed below within easy reach on a table or other stable surface:

- 1 Rebidose® autoinjector containing Rebif®
- Alcohol wipes/swabs or cotton balls and rubbing alcohol
- Small adhesive bandage strip (if needed)
- A biohazard (sharps) container (see Disposal section on page 28)

1.3) Wash your hands thoroughly with antibacterial soap.

1.4) Open the tray over a table or soft surface by peeling back the plastic covering and remove 1 Rebif® Rebidose® autoinjector. **Do not** remove the needle cap until you are ready to inject because the autoinjector could roll off the table and become unsterile.

1.5) Check the expiration date on the Rebidose® autoinjector label and its carton. If the medication has expired, **do not** use it.

1.6) Examine the contents of the syringe carefully through the transparent housing. The liquid should be clear or slightly yellow.

1.7) Inspect for cracks or breakage in the syringe or other parts. **Do not** use the Rebif® Rebidose® autoinjector if it is cracked or broken or if the liquid is cloudy, discolored or contains particles.

Step 1: Prepare for your injection (continued)

1.8) Use an alcohol wipe to clean the injection site. Let your skin dry to prevent stinging during injection.

1.9) Hold the Rebidose® by the injector body (fig **a**) and pull off the needle cap.

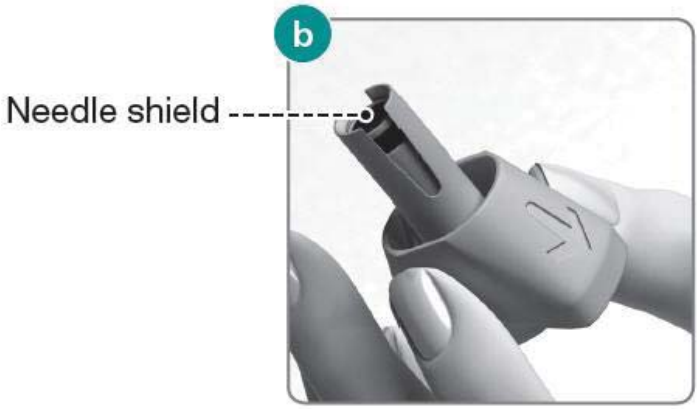
1.10) Look inside the needle cap to make sure you see a black needle shield inside the cap (fig **b**).

1.11) Dispose of the needle cap and proceed to the injection step without delay.

.

⚠ Warning

If the Rebidose® has been dropped more than 3 feet, or if it looks damaged for any reason, **do not** use it. Instead, dispose of it in an acceptable biohazard (sharps) container and use a new Rebidose® autoinjector.



Step 2: Administer your injection

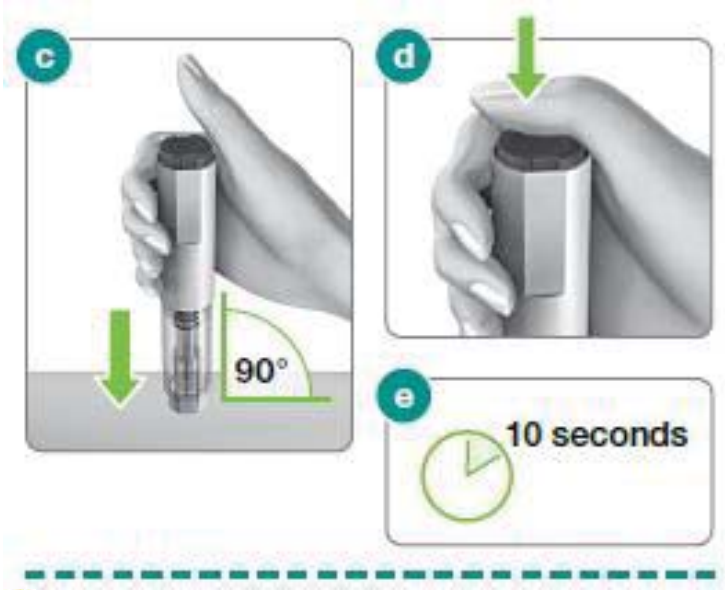
2.1) Hold the Rebidose® autoinjector in your palm with your thumb above the injector button.

2.2) Place the Rebidose® upright with the needle end flat against your skin at a 90° angle. Push the Rebidose® against your skin until you feel resistance; this action unlocks the injector button (fig **c**).

2.3) Keep the Rebidose® pressed firmly against the skin and use your thumb to push the injector button (fig **d**). You will hear a click, which means the injection has begun.

2.4) Keep the Rebidose® pressed firmly against your skin for at least 10 seconds while the medication is dispensed (fig **e**).

If you have any problems, contact MS LifeLines at 1-877-447-3243.



Caution

If the injection does not start, release the injector button and make sure that the Rebidose® is still pressed firmly against your skin. Then push firmly on the injector button, listening for the click that indicates the start of the injection.

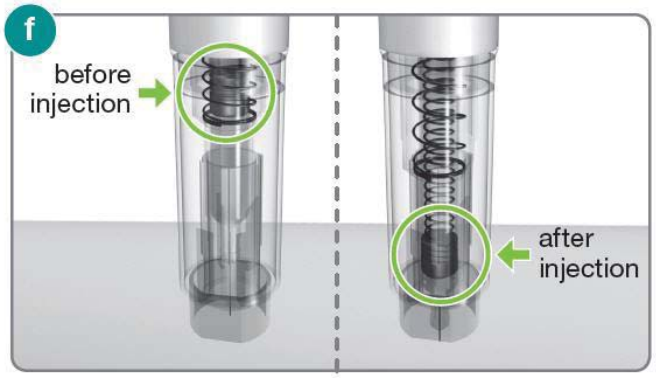
Step 3: Finish your injection

3.1) Before lifting the Rebidose® from your skin, make sure that the syringe plunger has moved to the bottom and that the entire dose has been injected (fig **f**).

3.2) Lift the Rebidose® from the injection site. The safety guard slides down and locks into place to protect you from the needle (fig **g**). If any liquid is left in the syringe or if you have any other problems, contact your health care provider or MS LifeLines at 1-877-447-3243.

Do not try to put the needle cap on the used Rebidose® autoinjector. It is no longer needed.

3.3) If desired, use a small adhesive bandage to cover the injection site.



Disposal

1) Put your used Rebidose® autoinjectors in a FDA-cleared sharps disposal container right away after use (fig **h**). Do not throw them away (dispose of) in your household trash.

2) 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 and stable during use;
- leak-resistant; and
- properly labeled to warn of hazardous waste inside the container.

3) When your sharps disposal container is almost full, you will need to follow your community guidelines for the correct way to dispose of it. There may be state or local laws about how you should throw away used needles and syringes.
For more information about safe sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

4) 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.

Disposal (continued)

Caution

Always keep the biohazard (sharps) container out of the sight and reach of children.

Warning

- **Do not** insert your fingers into the opening of the safety guard.
- **Do not** try to re-use a Rebidose® single-use autoinjector that has already been used.
- Adhere to proper disposal procedures to avoid a needle stick injury.

Storage

- Each Rebidose® autoinjector contains a single dose of Rebif®.
- Store Rebidose® autoinjectors in the refrigerator between 36°F and 46°F (2°C to 8°C). **Do not freeze**. If a refrigerator is not available, Rebidose® may be stored between 36˚F and 77˚F (2˚C to 25˚C) for up to 30 days away from heat and light.
- **Do not** put them in or near the freezer compartment. **Do not** inject Rebif® that you know or suspect has been frozen.
- Keep the Rebidose® in its packaging and only open one when you need it. Refer to the Rebif® drug package insert and medication guide for specific storage guidelines.

Travel

- When you travel, take 3 Rebidose® autoinjectors with you for each week of your trip. Take some extra in case you are away for longer than expected.

- Remember to pack an empty biohazard (sharps) container for proper disposal.

- When traveling by air, always carry Rebidose® autoinjectors in your hand luggage because the aircraft luggage compartment can be very cold and the Rebif® could freeze.

- It is safe to pass Rebidose® autoinjectors through x-ray machines, but you may need a note from your health care provider to allow you to carry them aboard an airplane.

- Prior to traveling, always check with your airline and your health care provider about bringing injectable medication with you.

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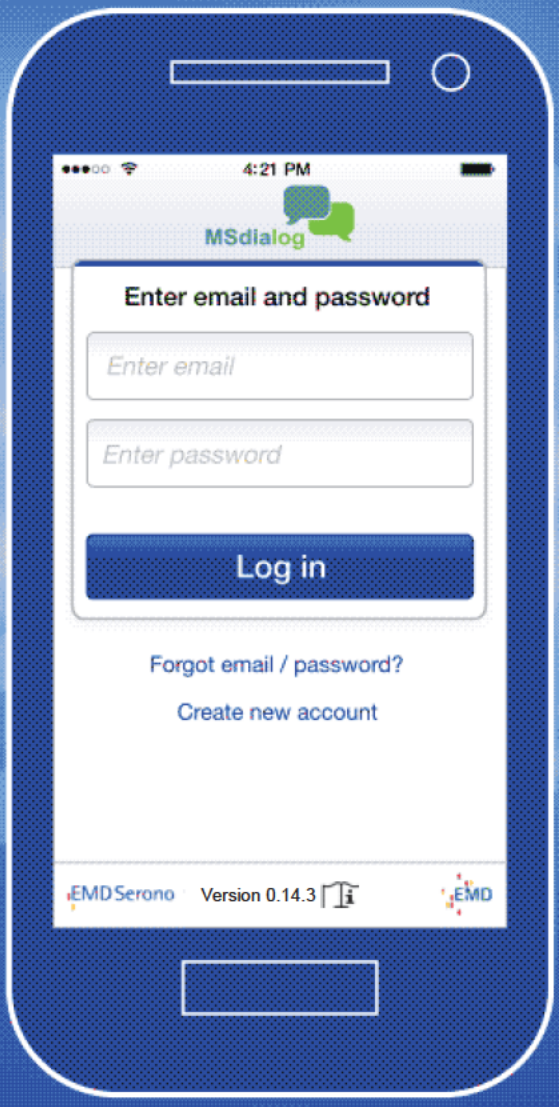
This Instructions for Use has been approved by the Food and Drug Administration.

Version: September 27, 2016
Manufactured for: EMD Serono, Inc.
Rockland, MA 02730 U.S. Lic. 1773
MS LifeLines: 1-877-447-3243

MSdialog™
MOBILE APPLICATION
Instructions For Use



MDT-705_2015_09-USA-v02
Revision date: 09-2015

EMD Serono EMD

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Reference ID: 3991333

Introduction

Reference ID: 3991333

This manual contains instructions for using the MSdialog™ Mobile Application.

The screenshots and images in this document use sample data only. Screenshots may differ slightly in the layout and appearance from what you will see in your software because of the operating system you use, or other software differences.

Reference ID: 3991333

MSdialog™ Mobile Application is intended to help patients taking Rebif® manage their treatment schedule, medication reminders, and track their injection history.

This Application is intended for use by people who are 18 years old or older.

Reference ID: 3991333

NOTE:

This smartphone application is not intended to replace the care provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment.

Reference ID: 3991333

To use MSdialog™ Mobile Application you must have one of the following smartphones:

- iPhone 4 or above (with iOS 7.1 or above), or
- Android smartphone (Android 4.1 OS or above) with a minimum screen resolution of 480 by 854 pixels.
- At least 100 MB of available storage space is required on the smartphone.

Reference ID: 3991333

MSdialog™ Mobile Application enables you to manage your Rebif® treatment schedule and review medication information.

This smartphone application can send you injection reminders by presenting notifications on your smartphone when you are scheduled to deliver an injection.

Reference ID: 3991333

⚠ CAUTION:

- Never use the “Clear Data” option for this application in your smartphone’s application settings. This option will erase your profile data and injection history from your smartphone.

Reference ID: 3991333

MSdialog™ Mobile Application can help you collect and review information about your use of Rebif® injection device(s).

NOTE:

- This smartphone application does not affect how your Rebif® injection device works.
- The data stored in this smartphone application is not made available to anyone else, unless you choose to show it or leave your smartphone unlocked.

Reference ID: 3991333

If you have questions, concerns, recommendations, or difficulties using MSdialog™ Mobile Application, please contact your EMD Serono patient support program accessible via Help and Support.

For assistance with your medication, you may contact your doctor or:

MS LifeLines at
1-877-447-3243

Reference ID: 3991333

EMD Serono and its partners take every precaution to protect the personal information stored in MSdialog™ Mobile Application. To help protect the security of your personal information, remember to follow the recommendations below:

⚠ CAUTION:

- Protect your phone with a PIN lock to prevent unauthorized access to MSdialog™ Mobile Application and your account.

Reference ID: 3991333

- You will NOT receive reminders if you log out of the MSdialog™ Mobile Application after you have finished using it.
- DO NOT share your MSdialog™ Mobile Application password with anyone because it would give them access to MSdialog™ Mobile Application and your account.
- If you believe that others might have accessed your account, change your password as soon as possible.

Reference ID: 3991333

- To extend security, protect your smartphone using additional security controls (e.g. updated antivirus software, firewall settings, recent browser, etc.)
- Do not install the MSdialog Mobile Application on a “jailbroken” or “rooted” phone.
- Do not run an application that allows screen sharing while using the MSdialog Mobile Application.

Reference ID: 3991333

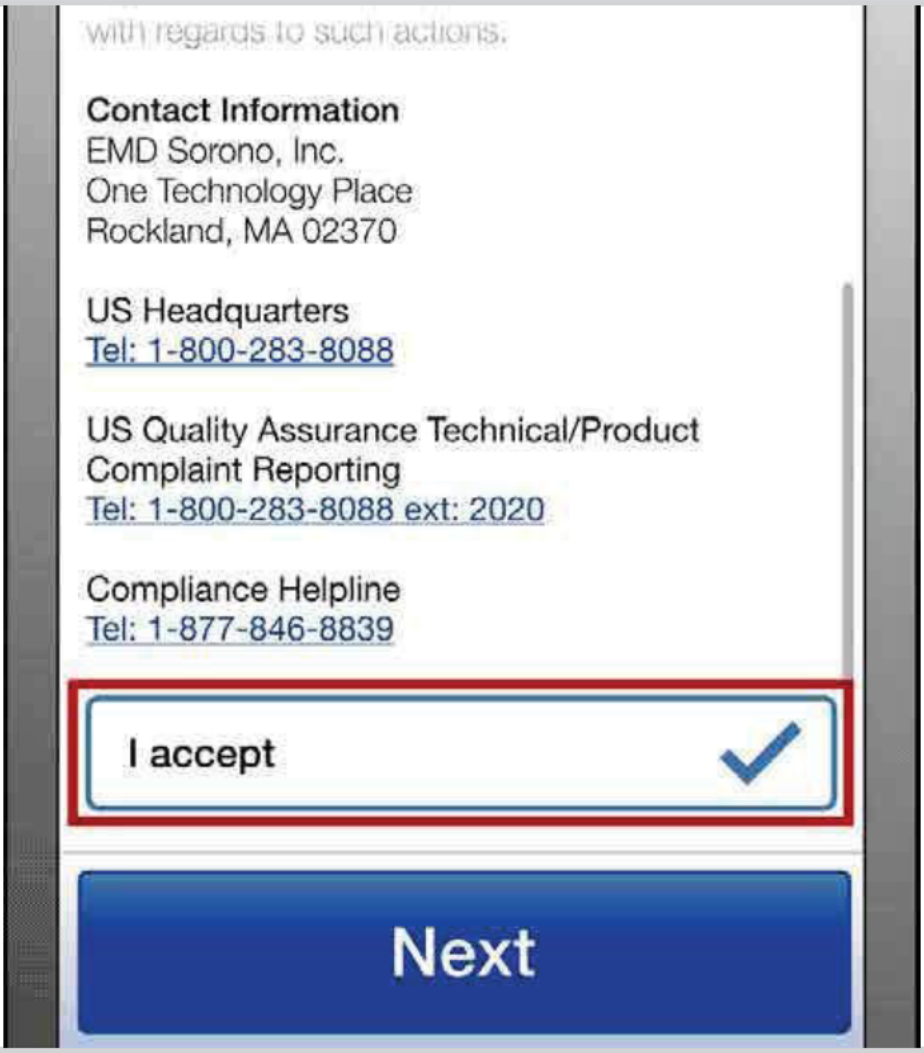
Getting Started

Reference ID: 3991333

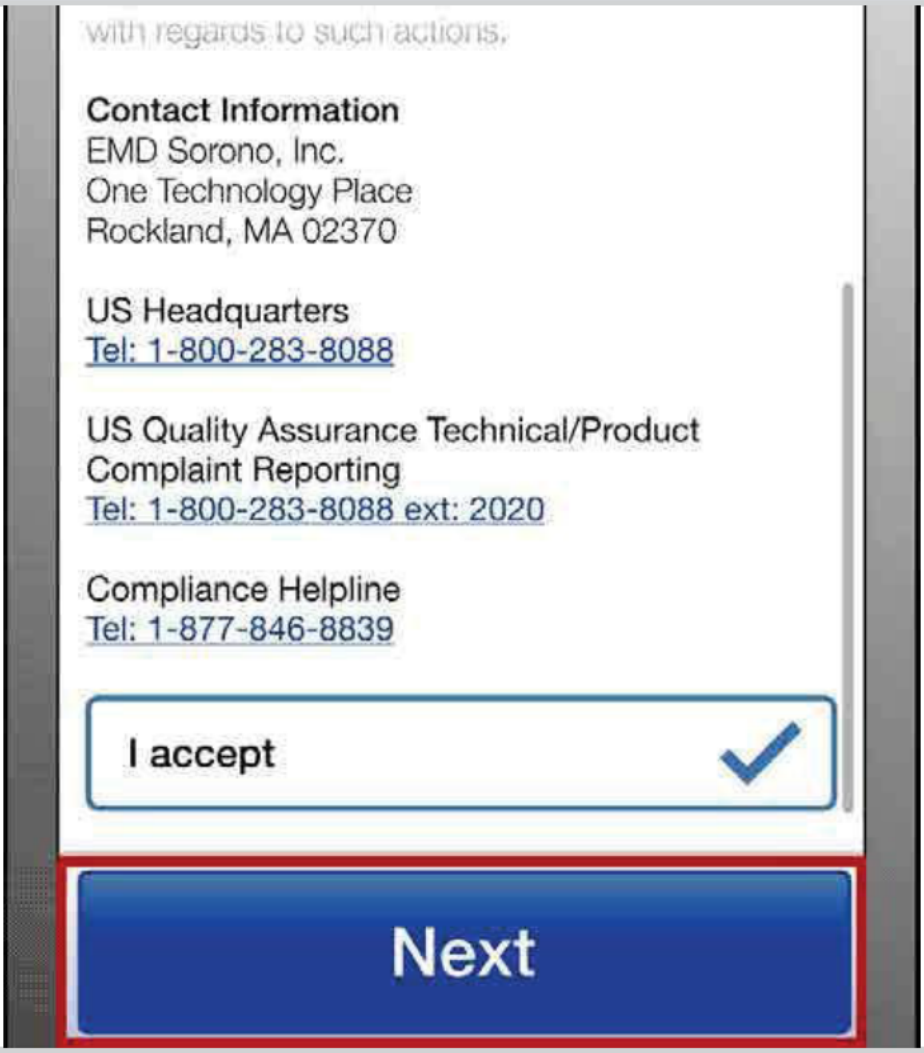
Getting Started
Create New Account

1. Tap the MSdialog™ Mobile Application icon on your smartphone. The Welcome to MSdialog™ screen appears.

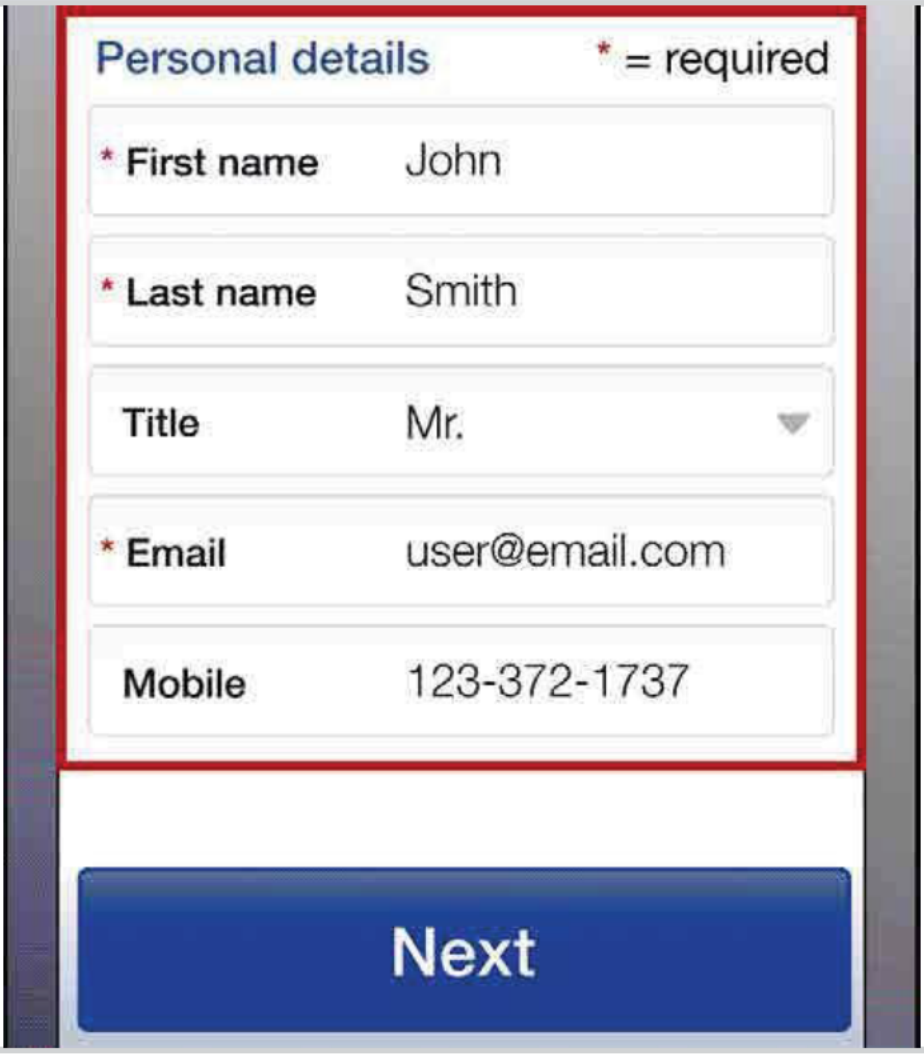
2. Tap the Create New Account button. The Terms and Conditions screen appears.



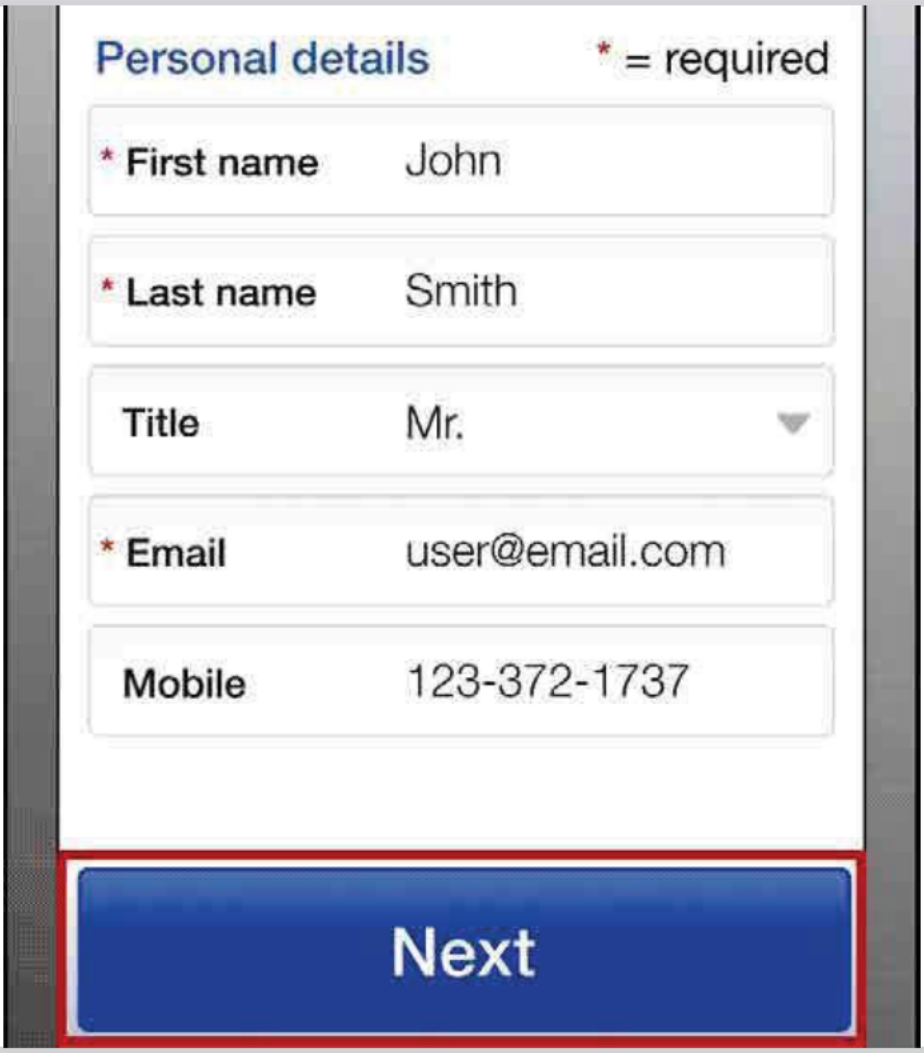
3. If you agree with the Terms and Conditions, tap the I accept button. You must accept all sections of the Terms and Conditions before you can proceed.



4. Tap the Next button. After accepting all sections of the Terms and Conditions, the New account screen will appear.

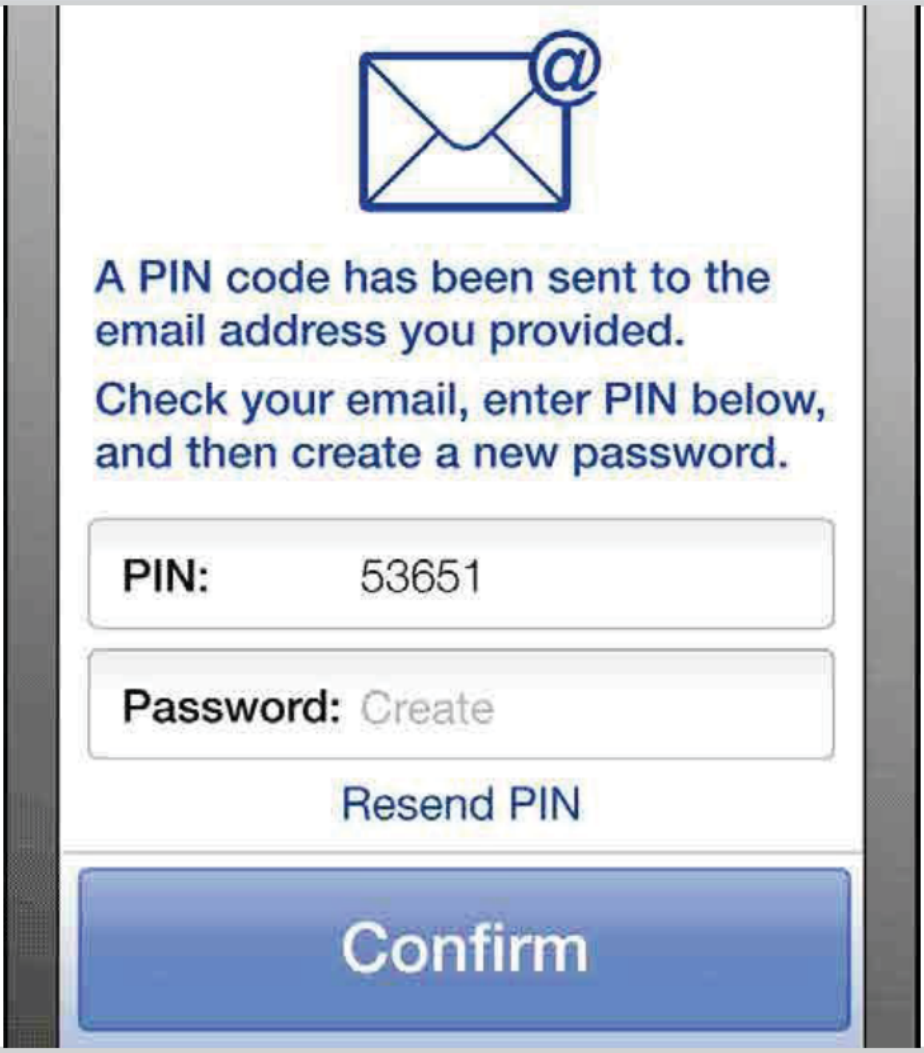


5. Enter your personal details in the relevant fields. Enter the email address at which you would like to receive a PIN code. Fields marked with a red asterisk are required.



6. Tap the **Next** button. The PIN code screen will appear.

7. Check your email for the MSdialog™ Mobile Application PIN code, then enter the PIN code into MSdialog™ Mobile Application.

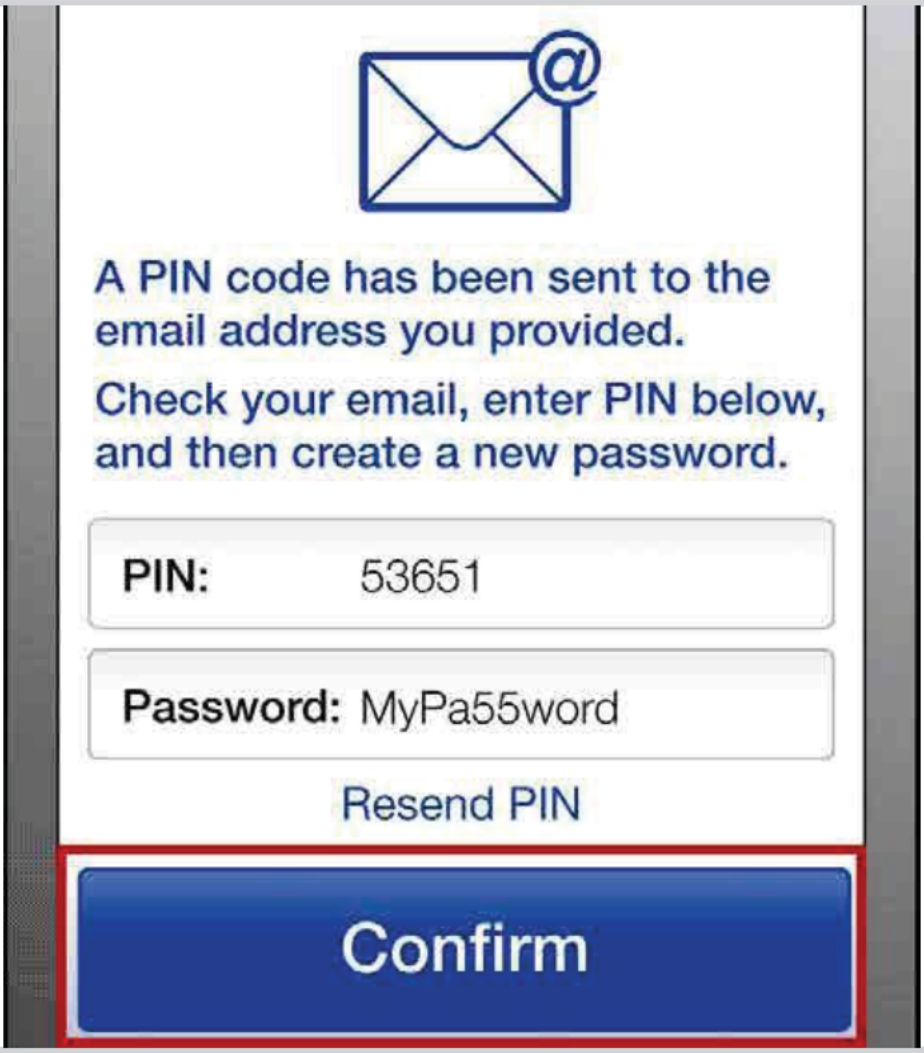


8. Think of a password and type it in the Password field.

NOTE:

If your password does not meet MSdialog™ Mobile Application password policy, the Application will remind you about the password minimum requirements.

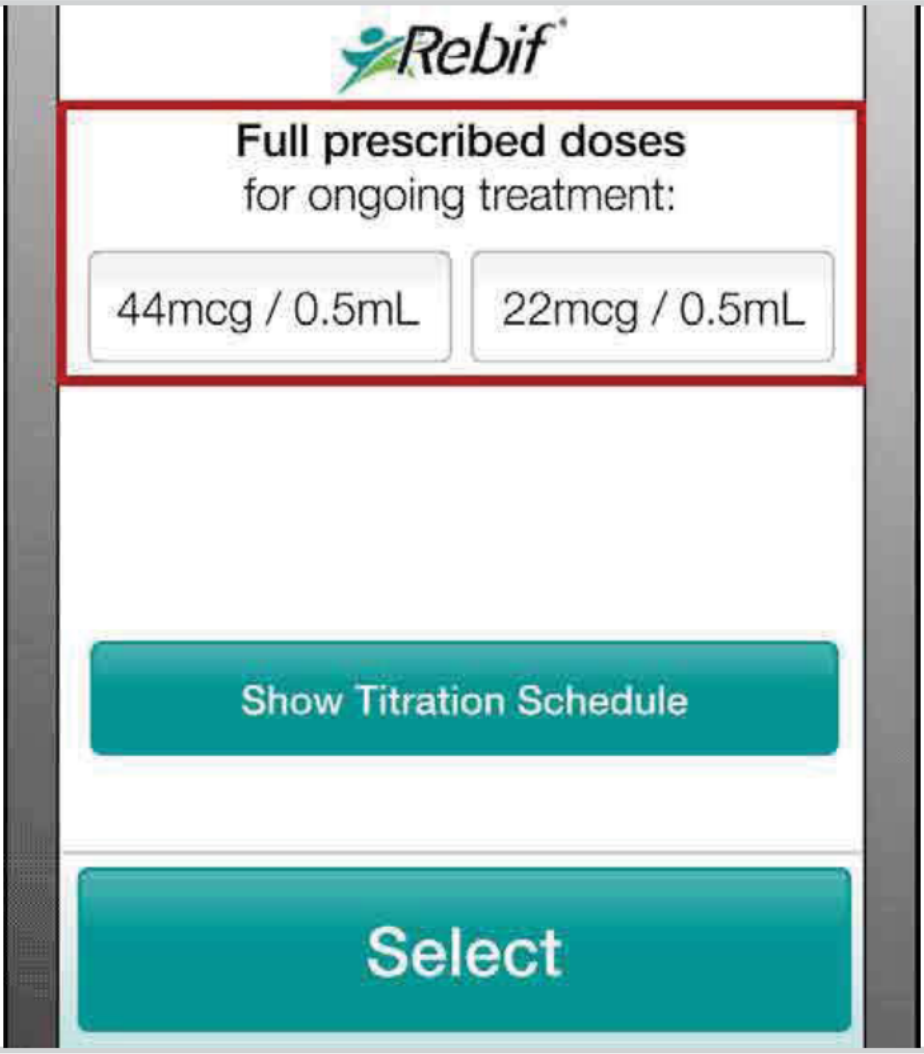
Reference ID: 3991333



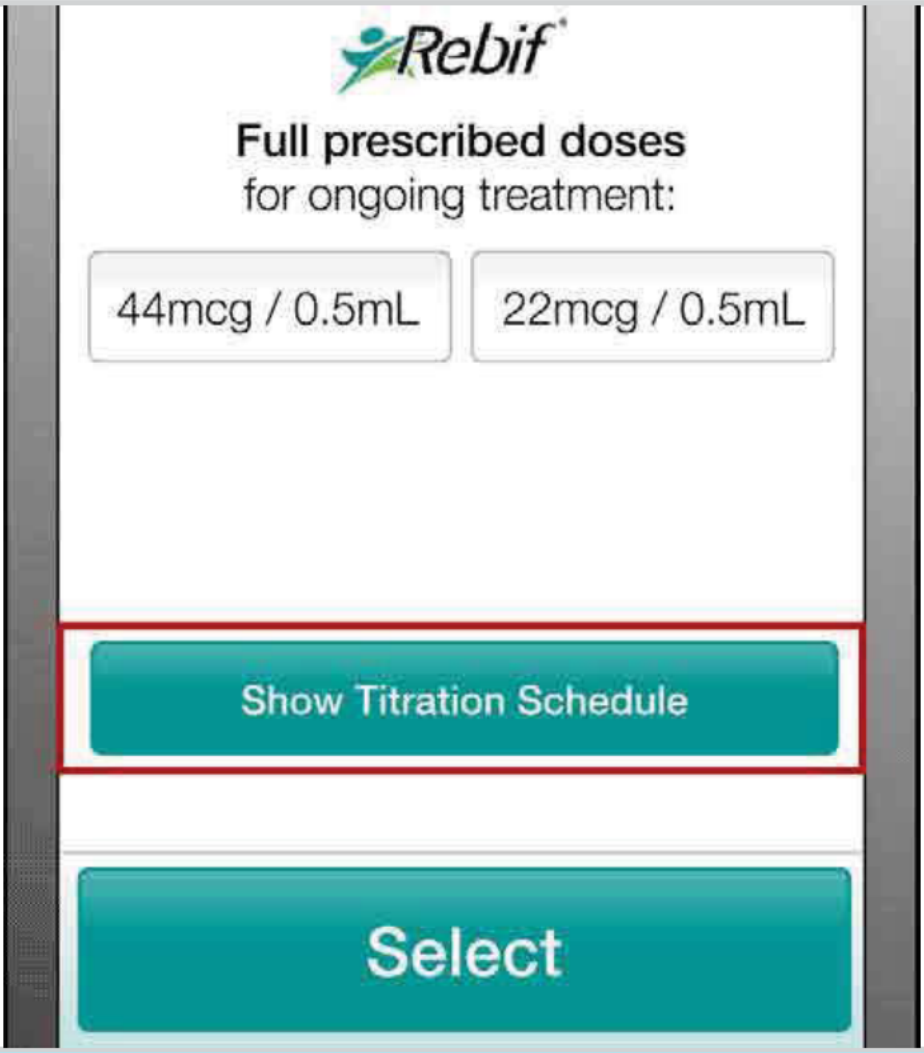
9. Tap the Confirm button. The Set Rebif® Settings screen will appear. You will receive an email confirming that your account has been created.

Reference ID: 3991333

Getting Started
Set Rebif® Settings



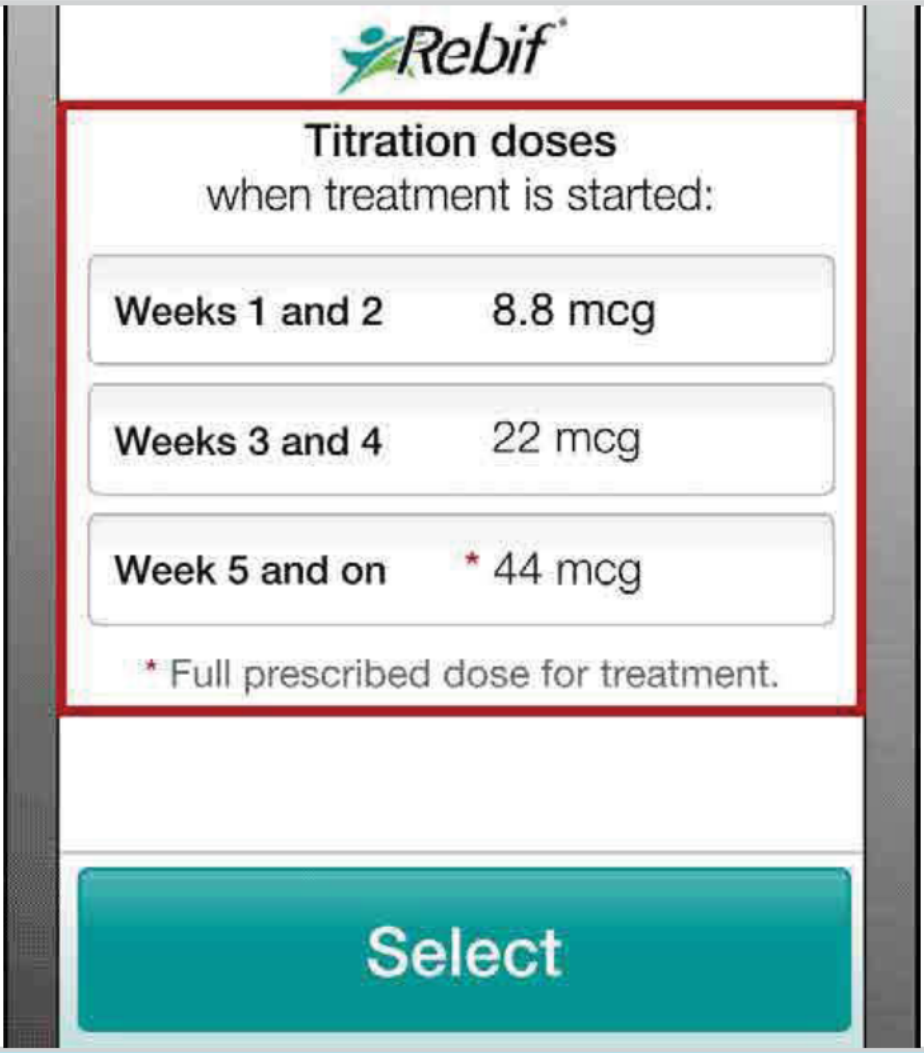
1. Select your full prescribed dose.



NOTE:

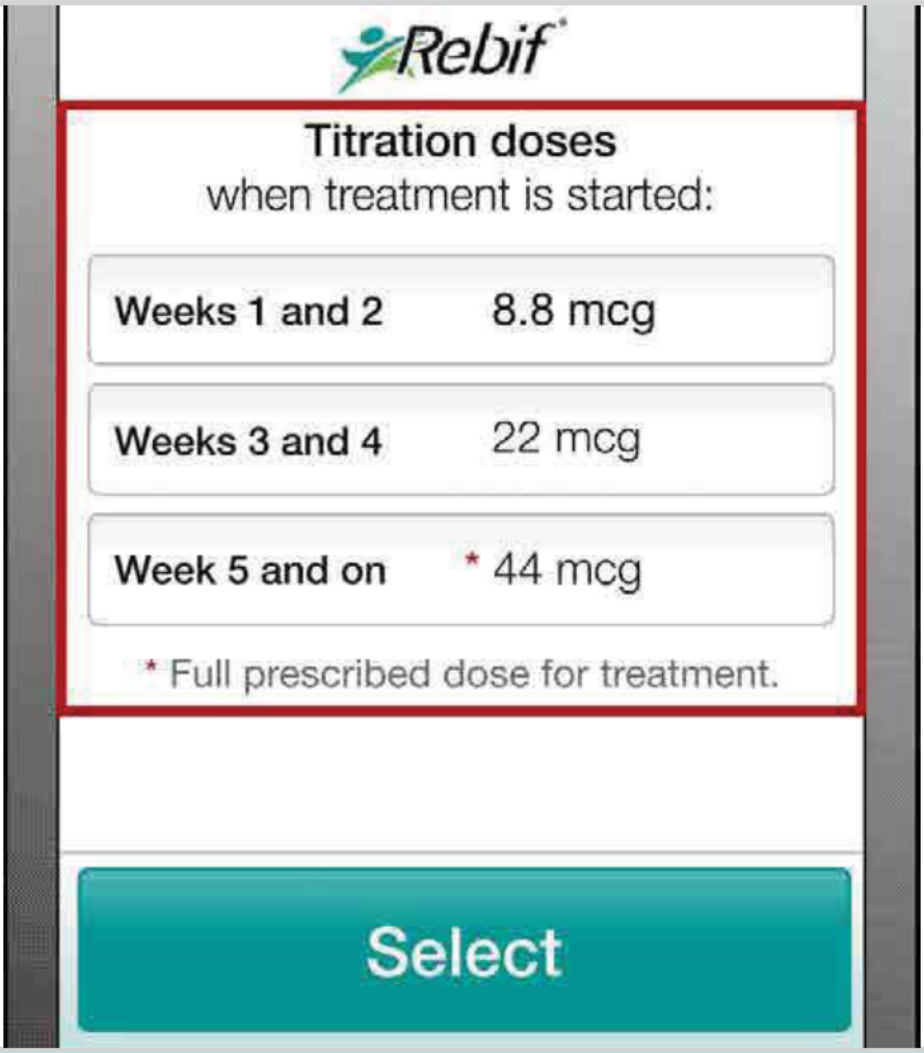
If you are on a titration schedule, tap the Show Titration Schedule button to modify your titration settings:

Getting Started
Set Rebif® Settings

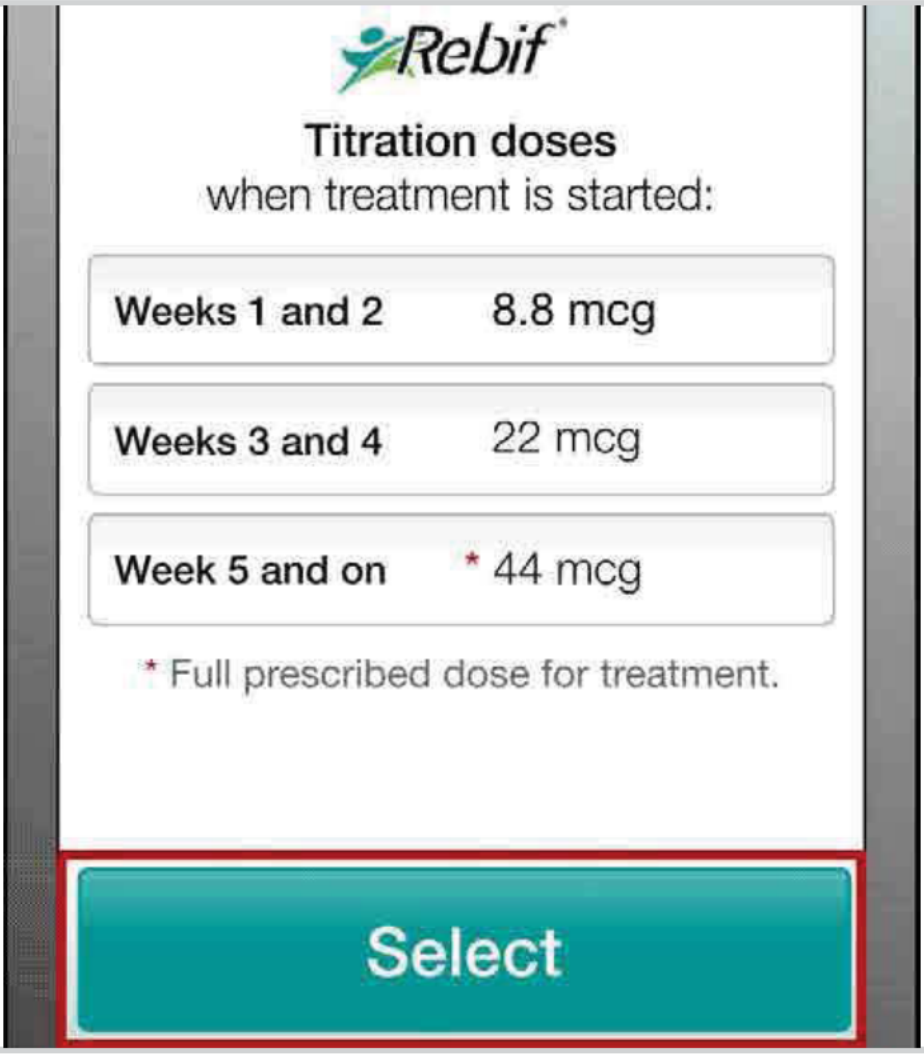


- Select Weeks 1 and 2 if you are in the first two weeks of your titration.
- Select Weeks 3 and 4 if you are in the third and fourth weeks of your titration.

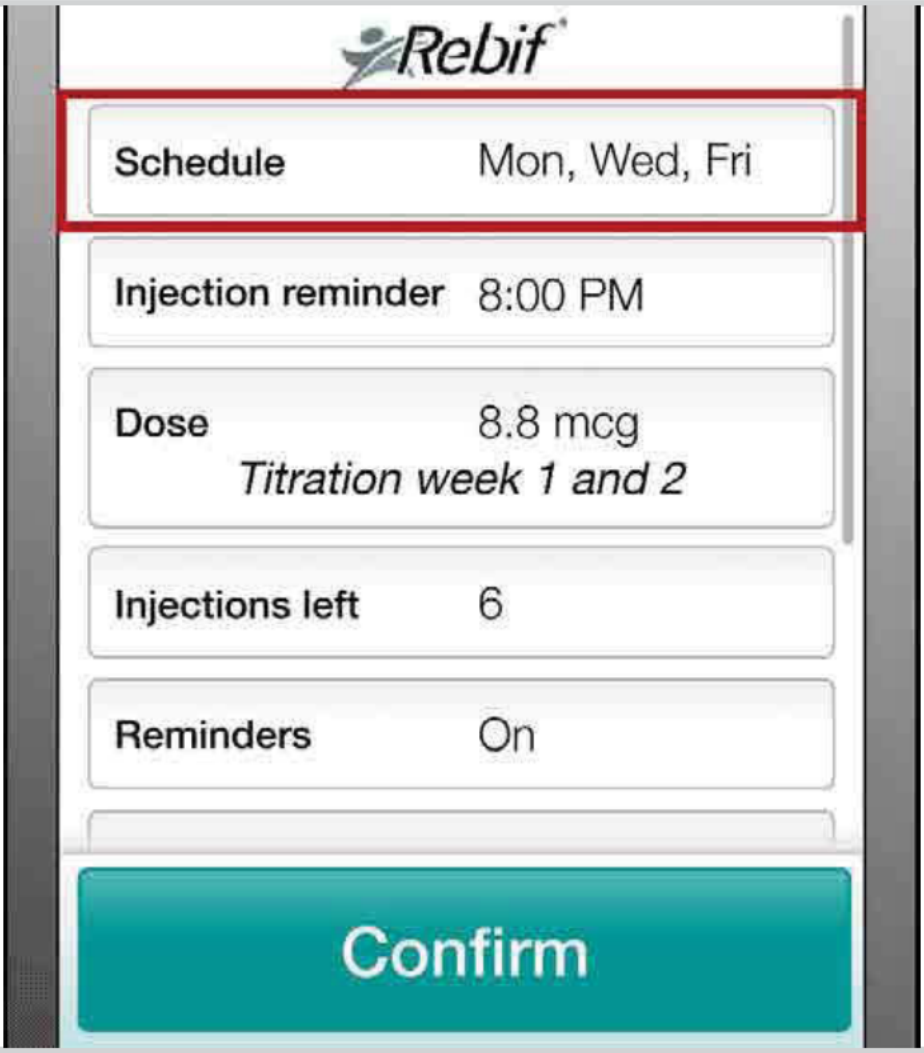
Getting Started
Set Rebif® Settings



- Select Week 5 and on if you completed your titration schedule and want to continue with your full prescribed dose.

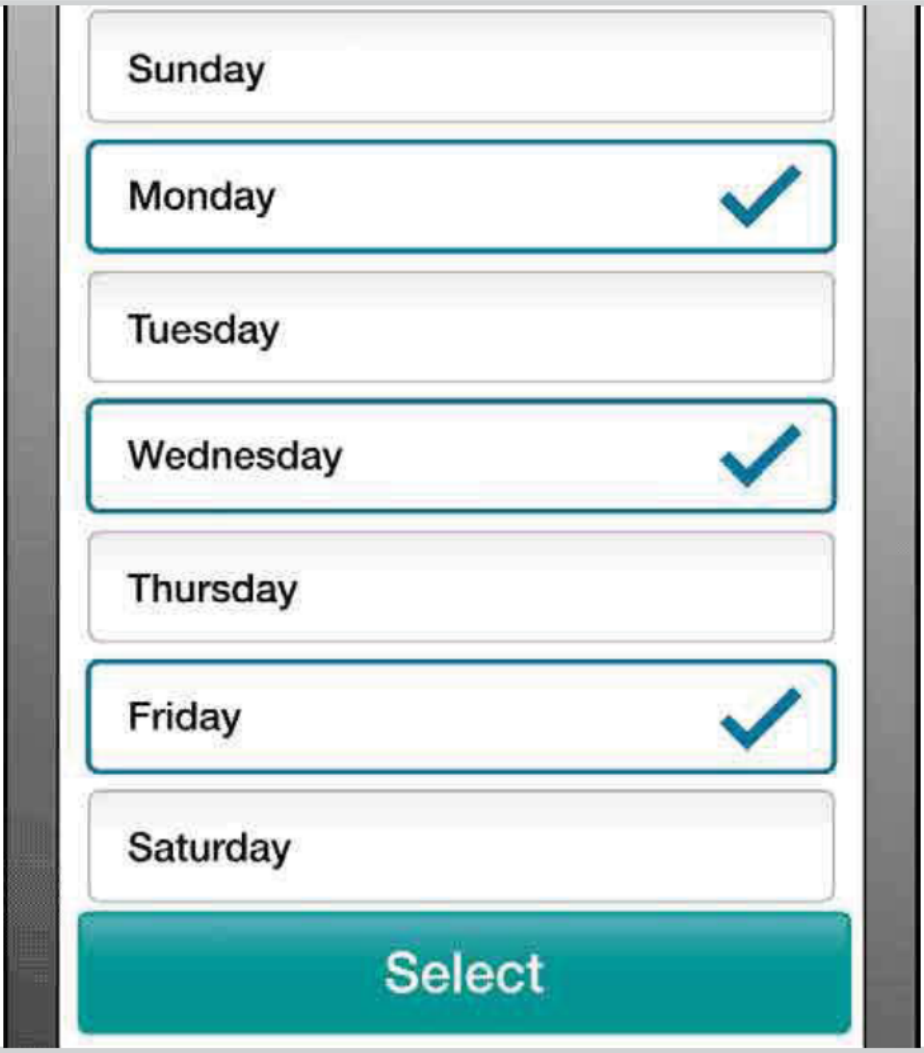


2. Tap the Select button. The Settings screen will appear.



3. Tap the Schedule button to select your preferred days. The Schedule page will appear.

Reference ID: 3991333

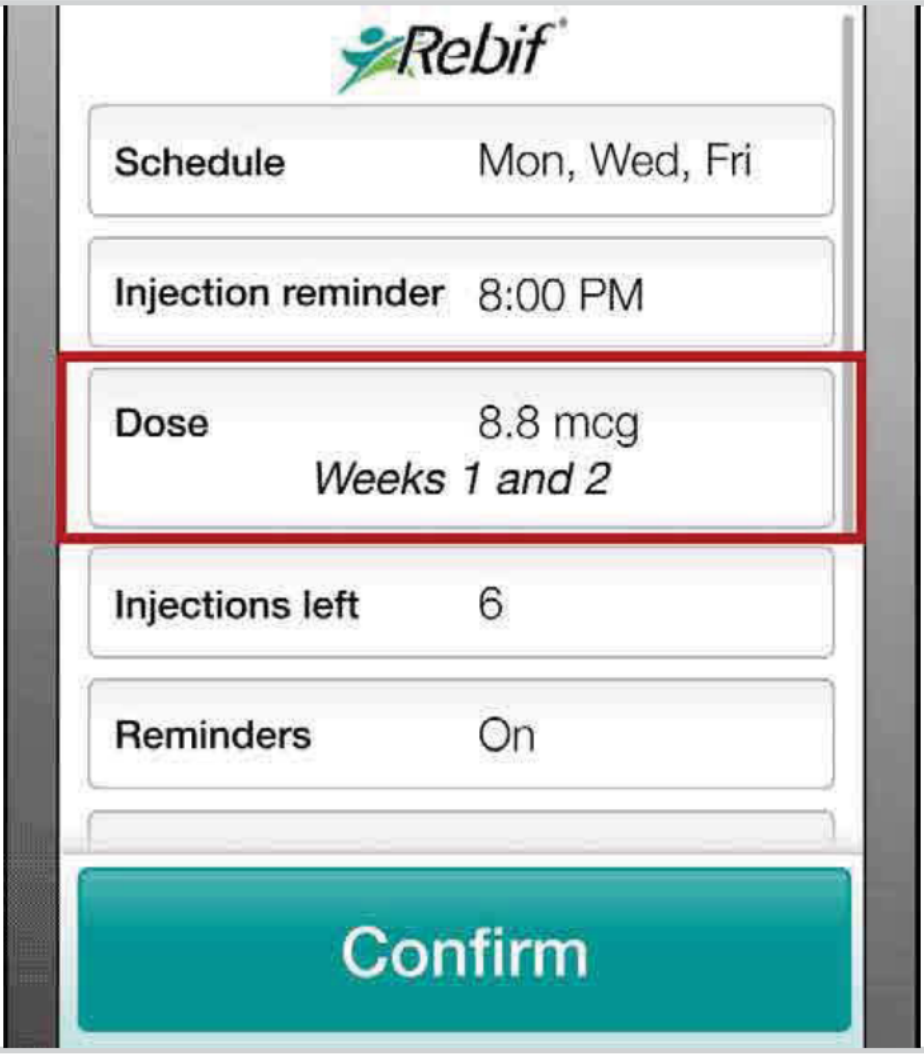


4. Select the 3 days that you will take your injections every week.

Reference ID: 3991333

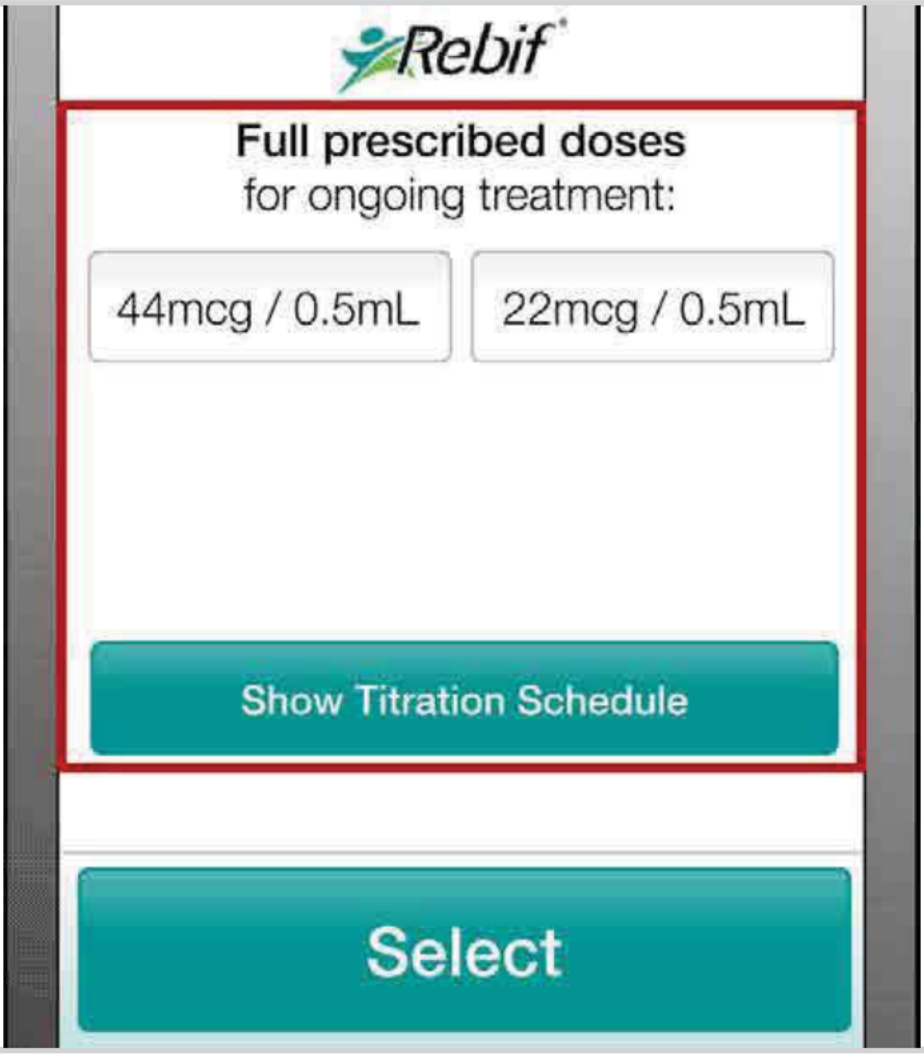
5. Tap the Injection reminder button to schedule the time at which your injection should occur.

Reference ID: 3991333



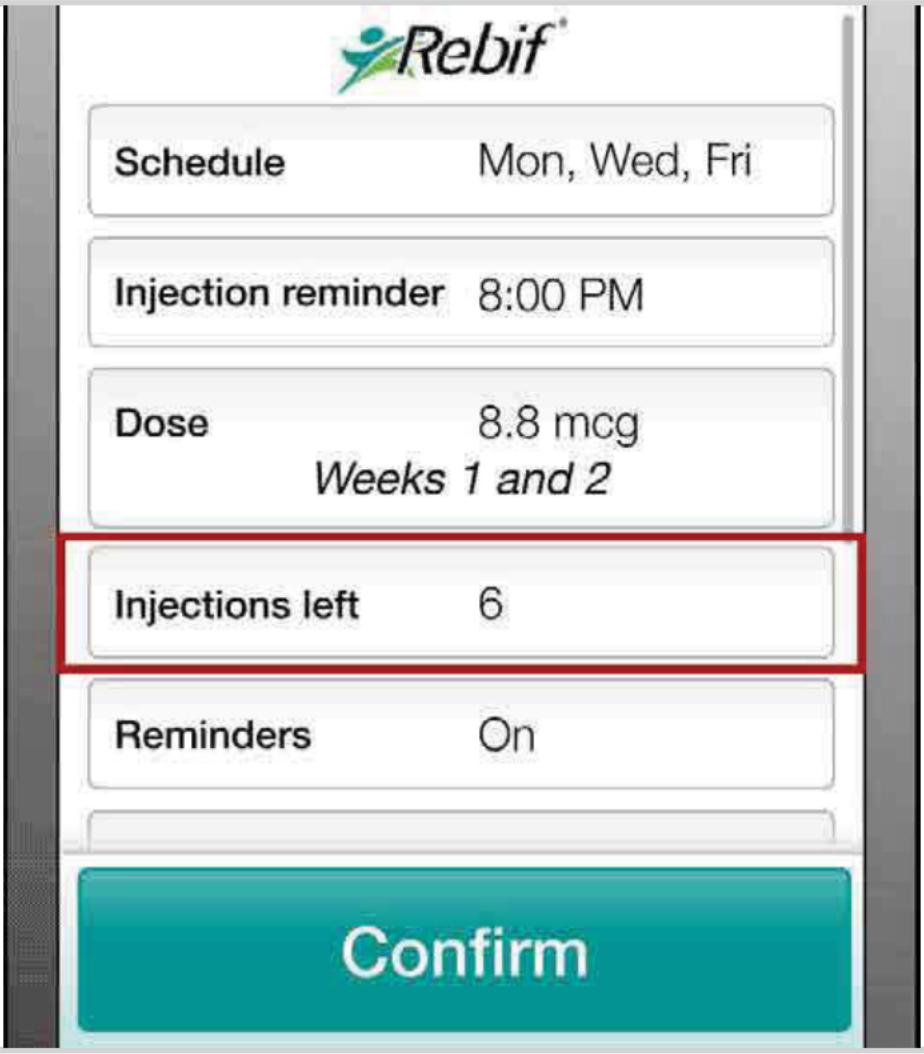
6. Tap the Dose button to adjust Dose and Titration Schedule. The Dose page will appear.

Reference ID: 3991333



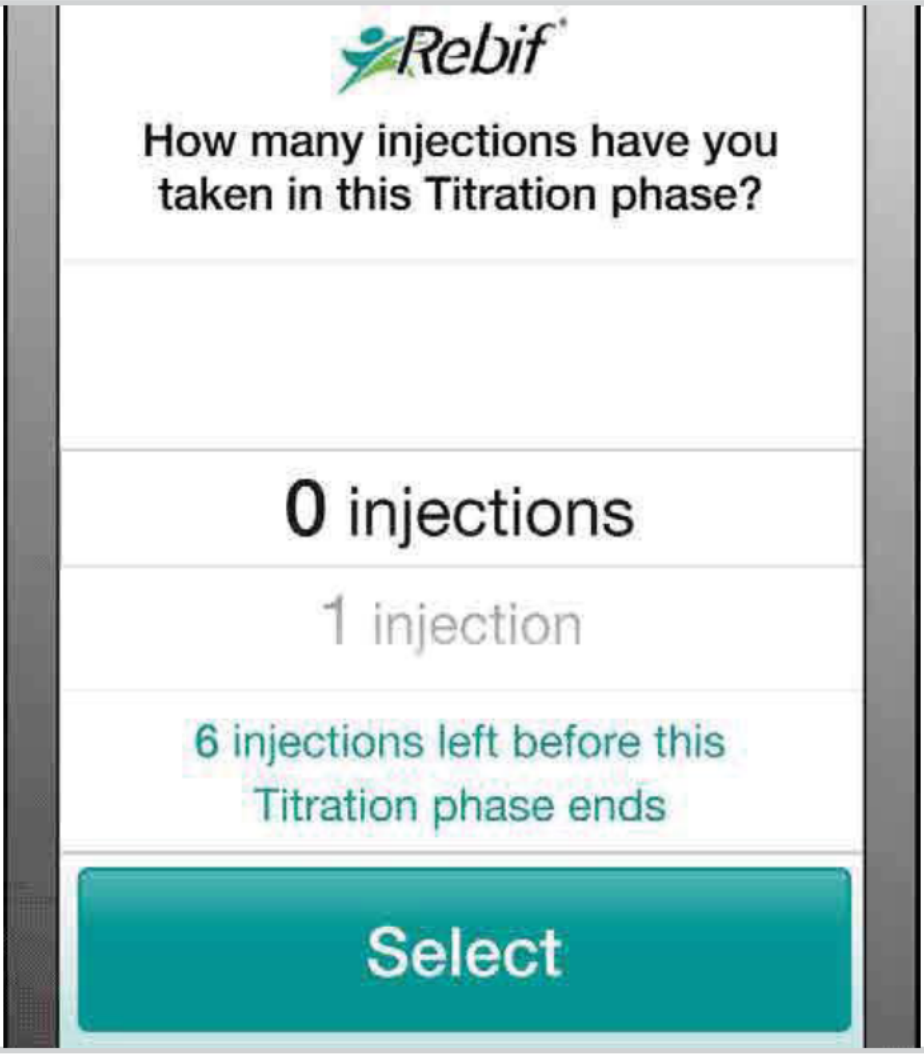
7. Adjust the Dose and the Titration Schedule for your treatment, based on the number of delivered injections.

Reference ID: 3991333



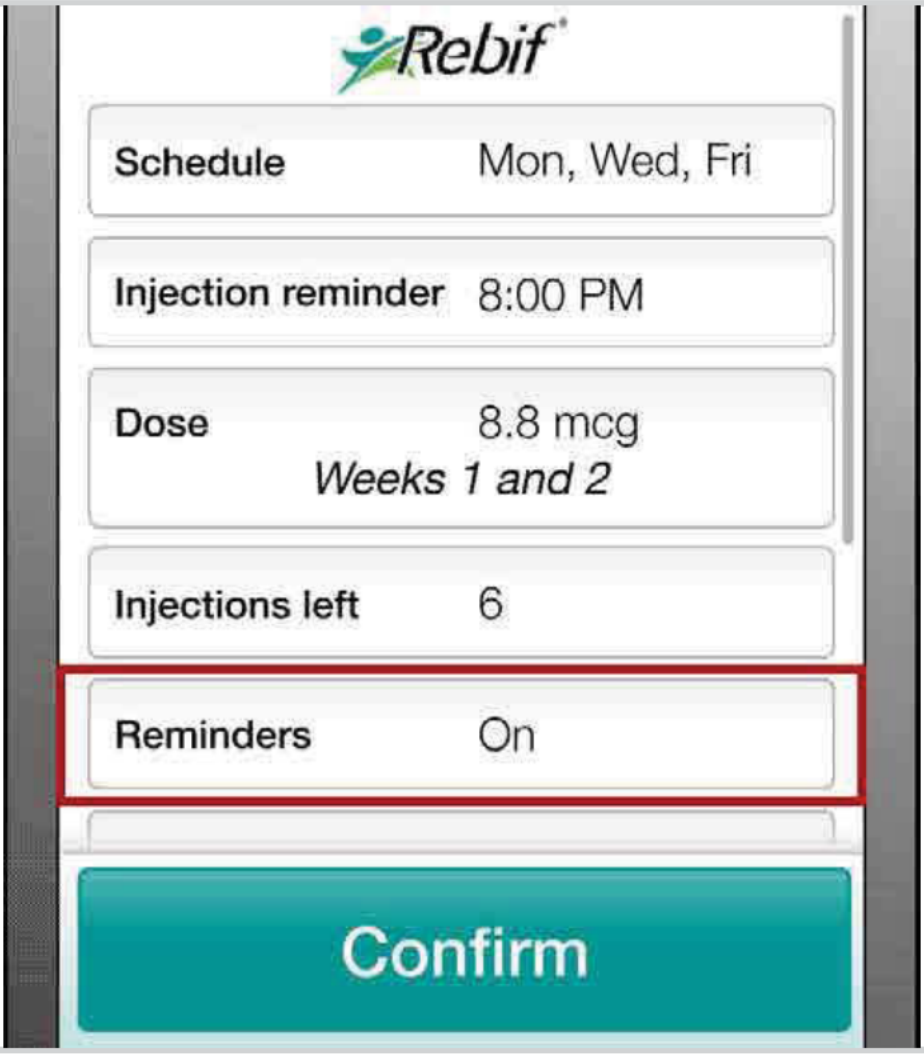
8. Tap the Injections left button. The Injections left page will appear.

Reference ID: 3991333



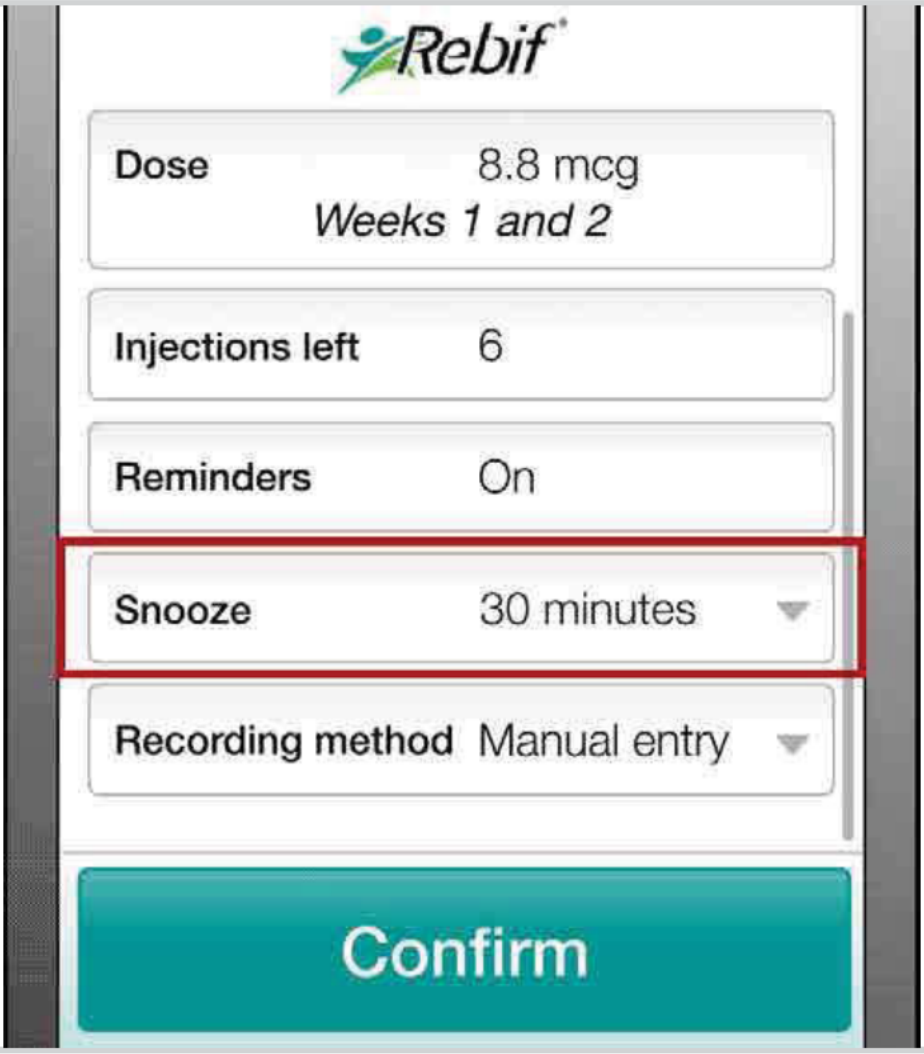
9. Adjust the number of injections left to complete your titration.

Reference ID: 3991333



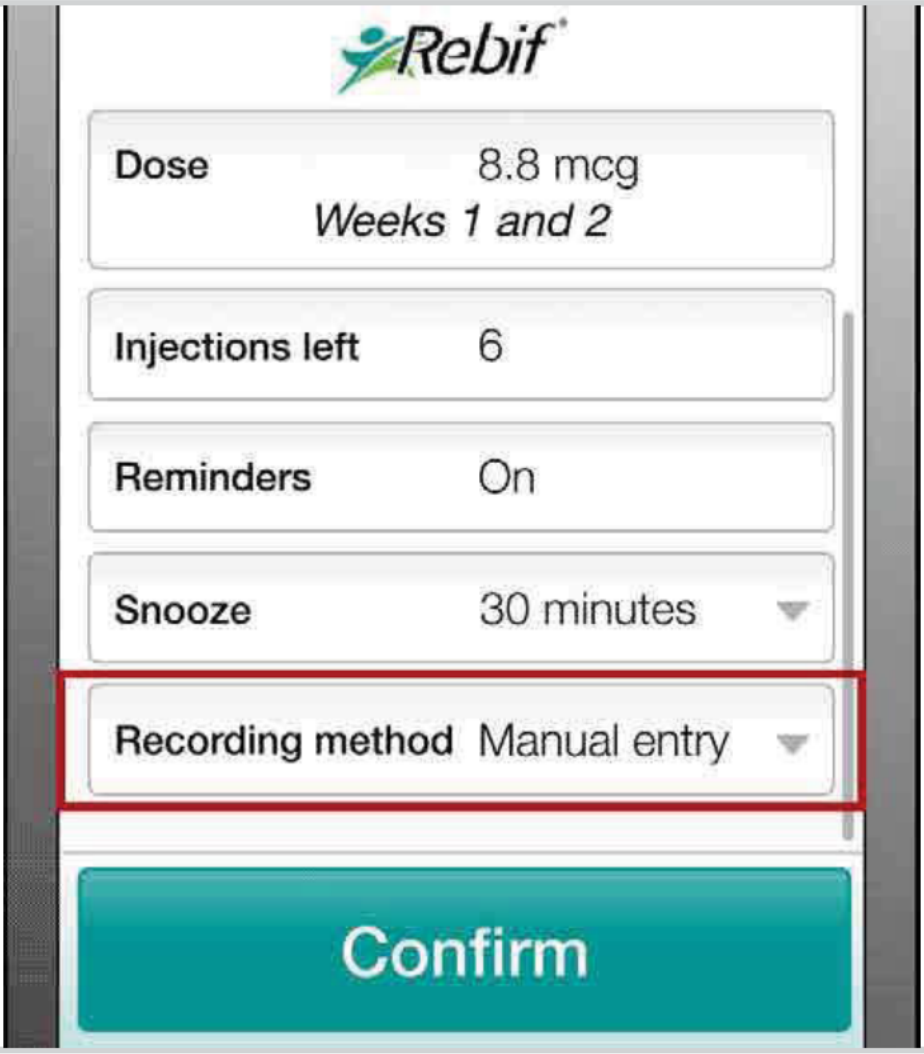
10. Tap the Reminders button to enable or disable the injection reminder notifications.

Reference ID: 3991333



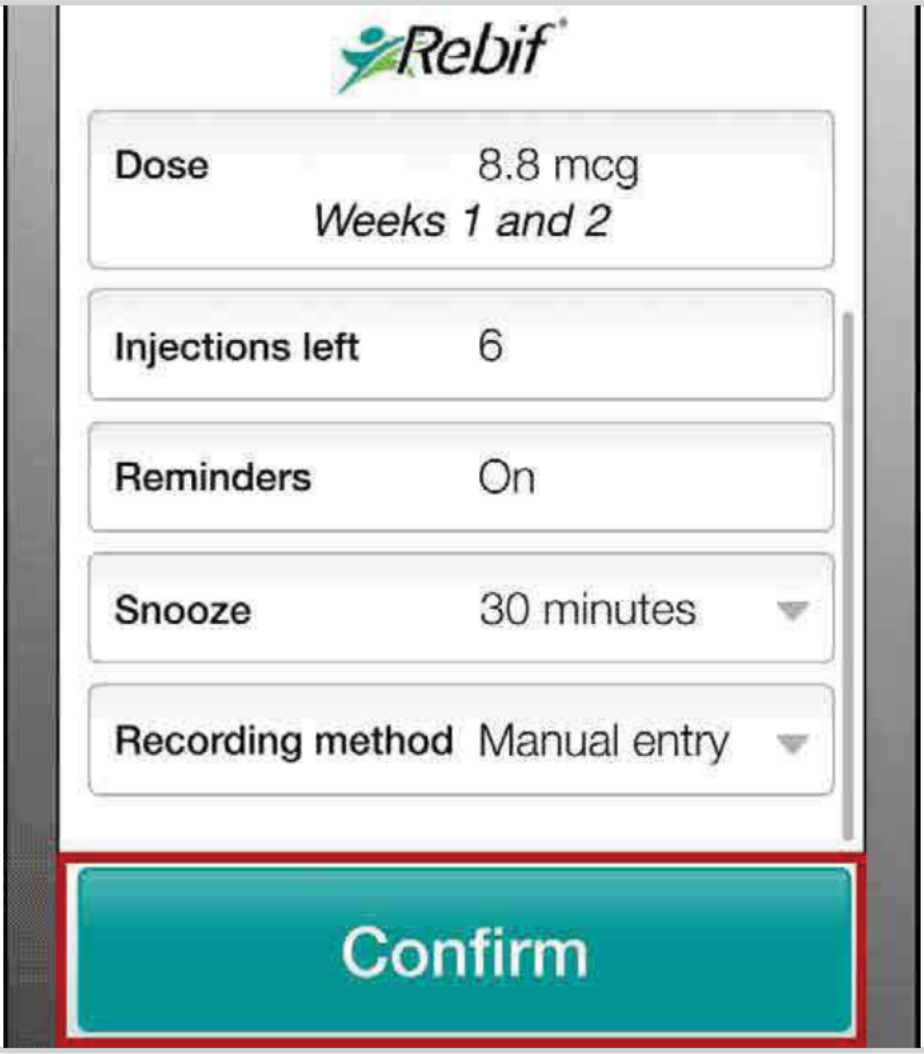
11. Tap the Snooze button to select the interval of time when the reminder alarm will repeat.

Reference ID: 3991333



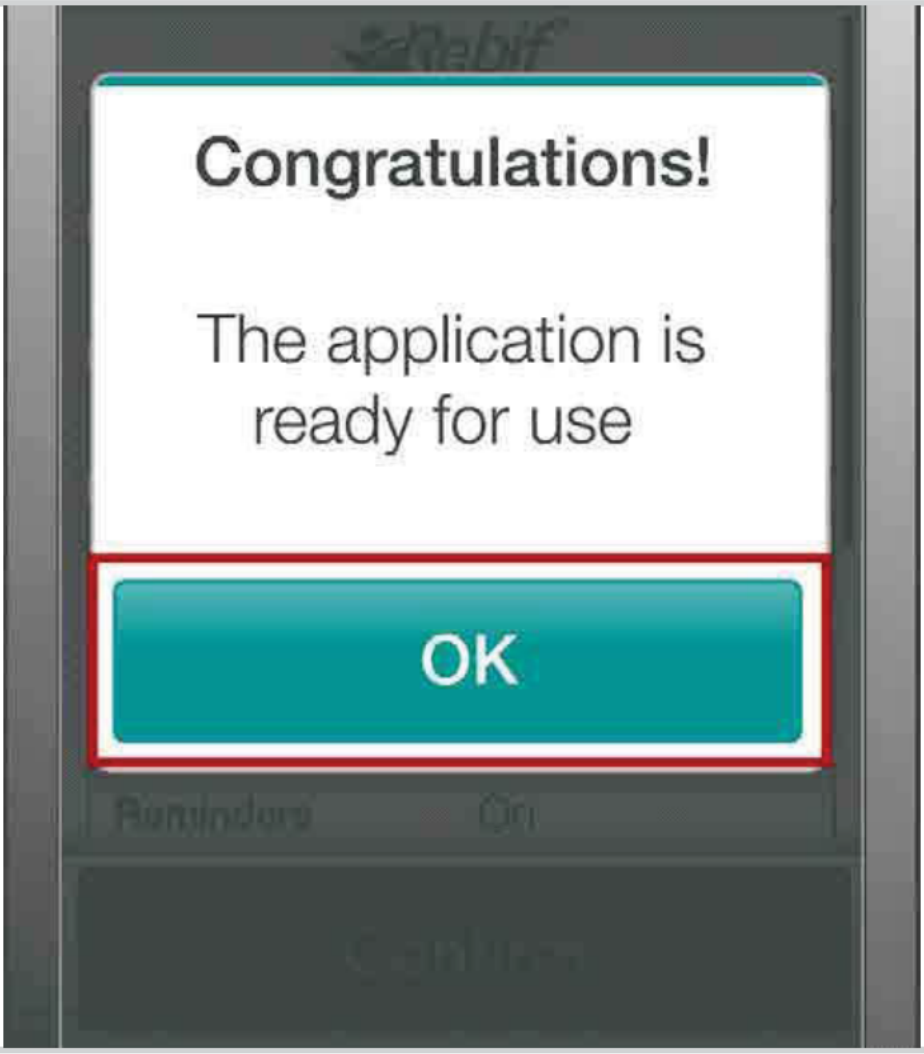
12. Tap the Recording method button to select your prefered data entry type, to record an injection into MSdialog™ Mobile Application.

Reference ID: 3991333



13. Tap the Confirm button. The Notification window will appear, indicating that your new account is ready.

Reference ID: 3991333



14. Tap the OK button. The Home screen will appear showing your medication and your next scheduled injection.

Reference ID: 3991333

After you log in to MSdialog™ Mobile Application the Home screen will appear. At the bottom of the Home screen is a row of four tabs:

1. Home tab
    - View upcoming scheduled injections
    - Record new injections

2. Calendar tab
    - View past and upcoming scheduled injections

Reference ID: 3991333

3. Reminders tab
    - Manage reminder settings for upcoming injections

4. More tab
    - Manage your profile settings
    - Get help
    - Log out
    - Review data stored
    - Close account

Reference ID: 3991333

Start Session

Reference ID: 3991333

Start Session
Introduction

This section explains how to:

- Log in to MSdialog™ Mobile Application
- Reset a forgotten password
- Retrieve a forgotten email address.

Reference ID: 3991333

Log In to MSdialog™

To log in to MSdialog™ Mobile Application you will need the email and password you used when you created an account.

Reference ID: 3991333

Start Session
Log In to MSdialog™

1. Tap the MSdialog™ Mobile Application icon on your smartphone. The Welcome to MSdialog™ screen appears.

Reference ID: 3991333

Start Session
Log In to MSdialog™

2. Type your email address and password in the relevant fields.

Reference ID: 3991333

Start Session
Log In to MSdialog™

3. Tap the Log in button.

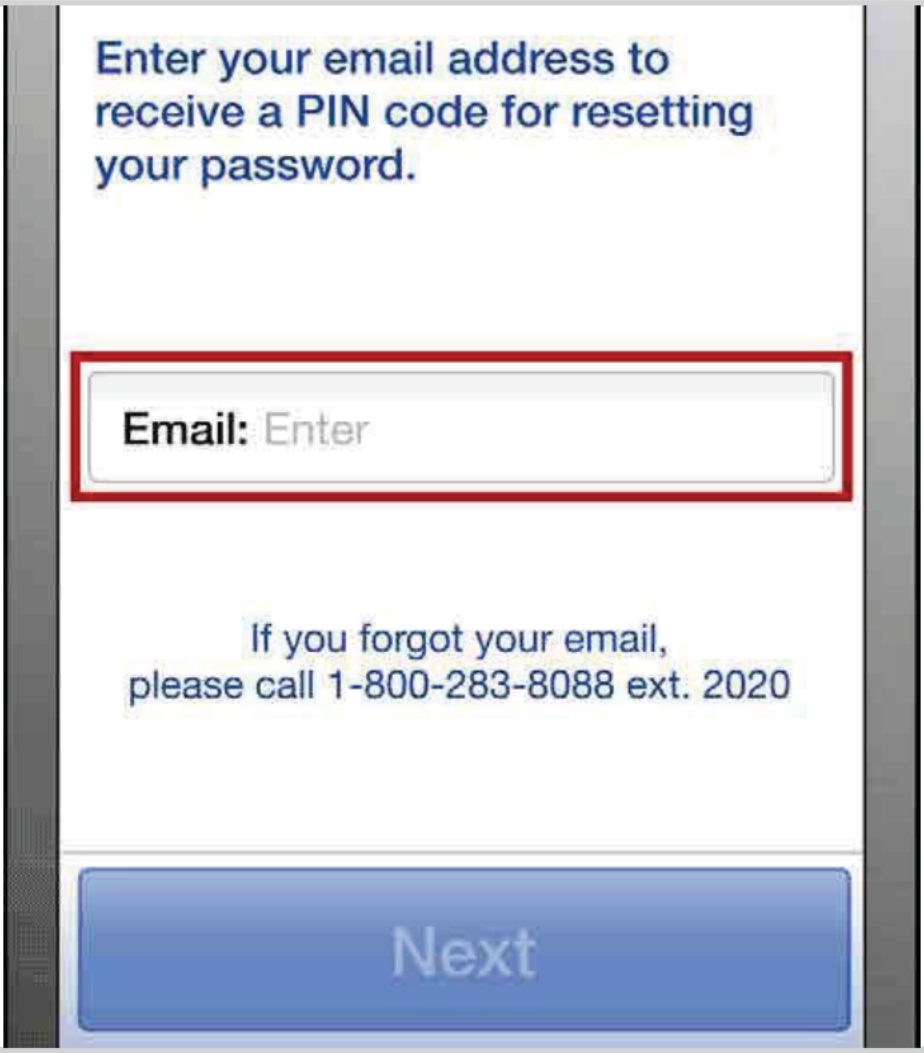
The Home screen will appear, indicating that you are logged in.

Reference ID: 3991333

Start Session
Reset a Forgotten Password

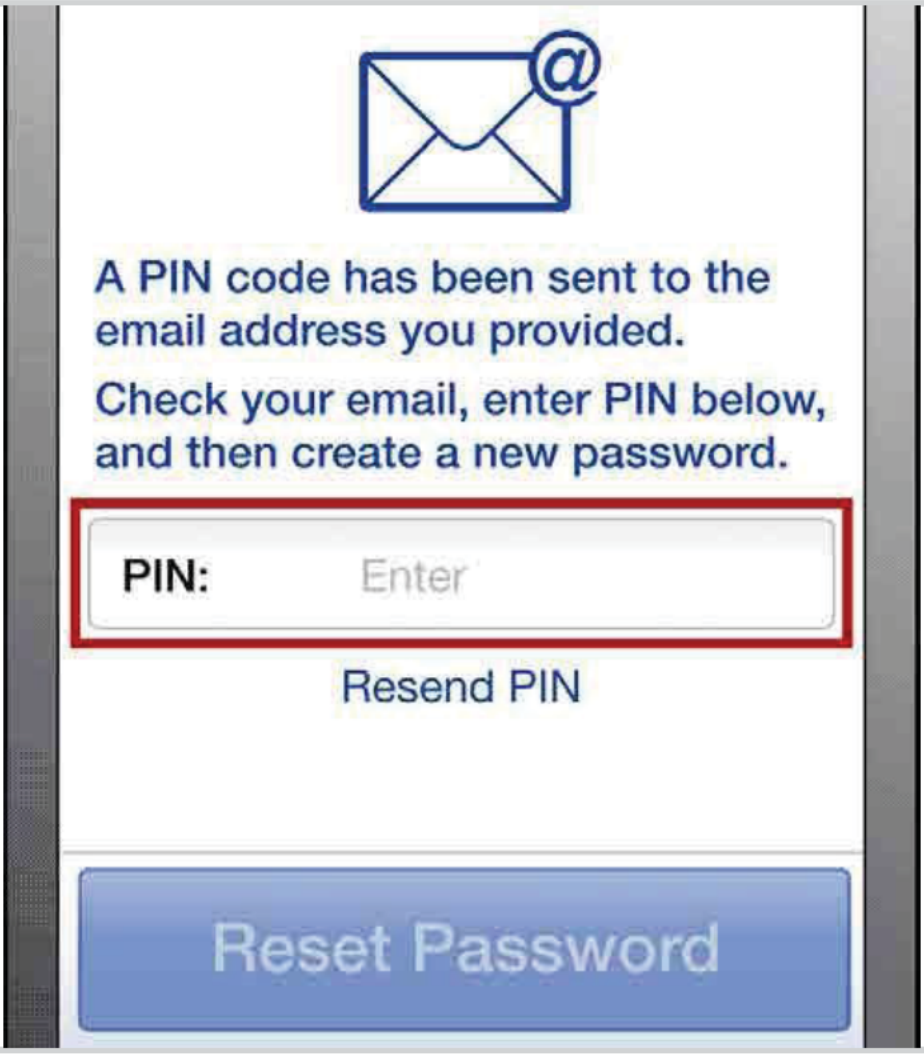
1. At the Log in screen, tap Forgot your email / password? button. The Reset password screen will appear.

Reference ID: 3991333



2. Enter the email address at which you would like to receive a PIN code, then tap the **Next** button.

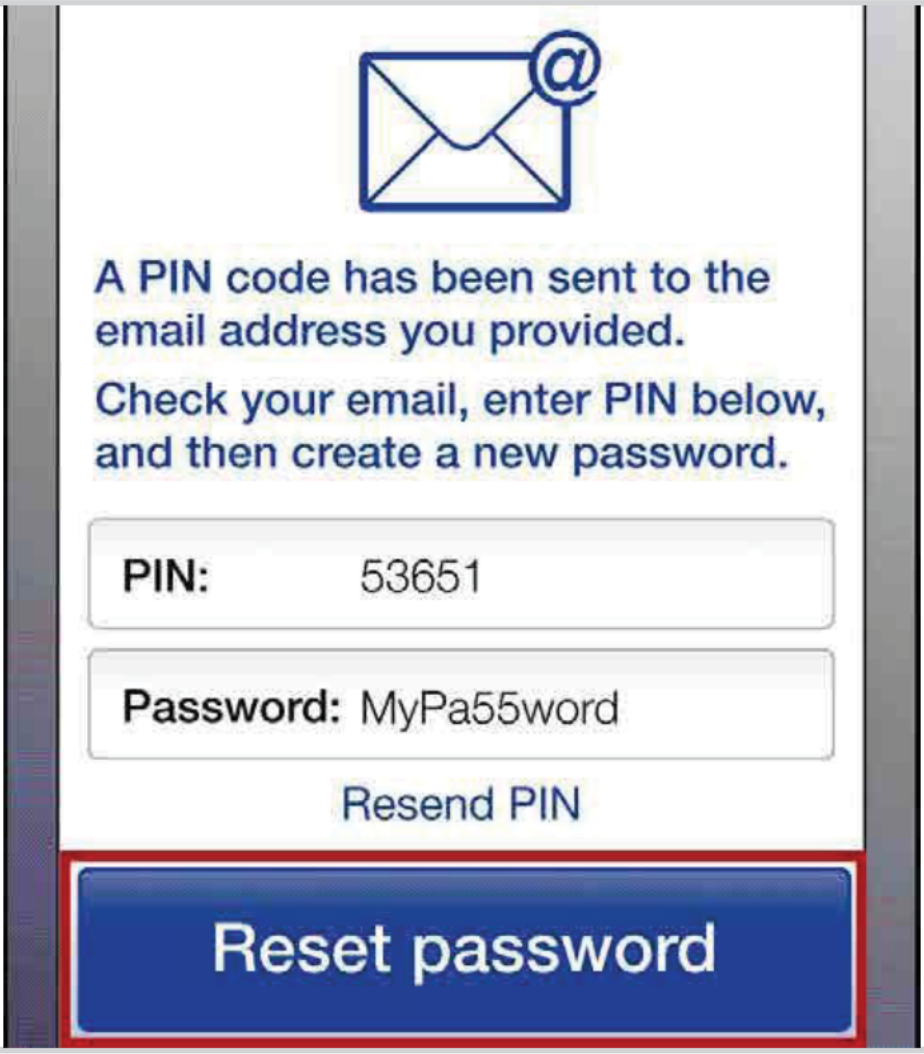
Reference ID: 3991333



3. Check your email for the MSdialog™ Mobile Application PIN code, then enter the PIN code into the application.

Reference ID: 3991333

4. Think of a new password and type it in the Password field.

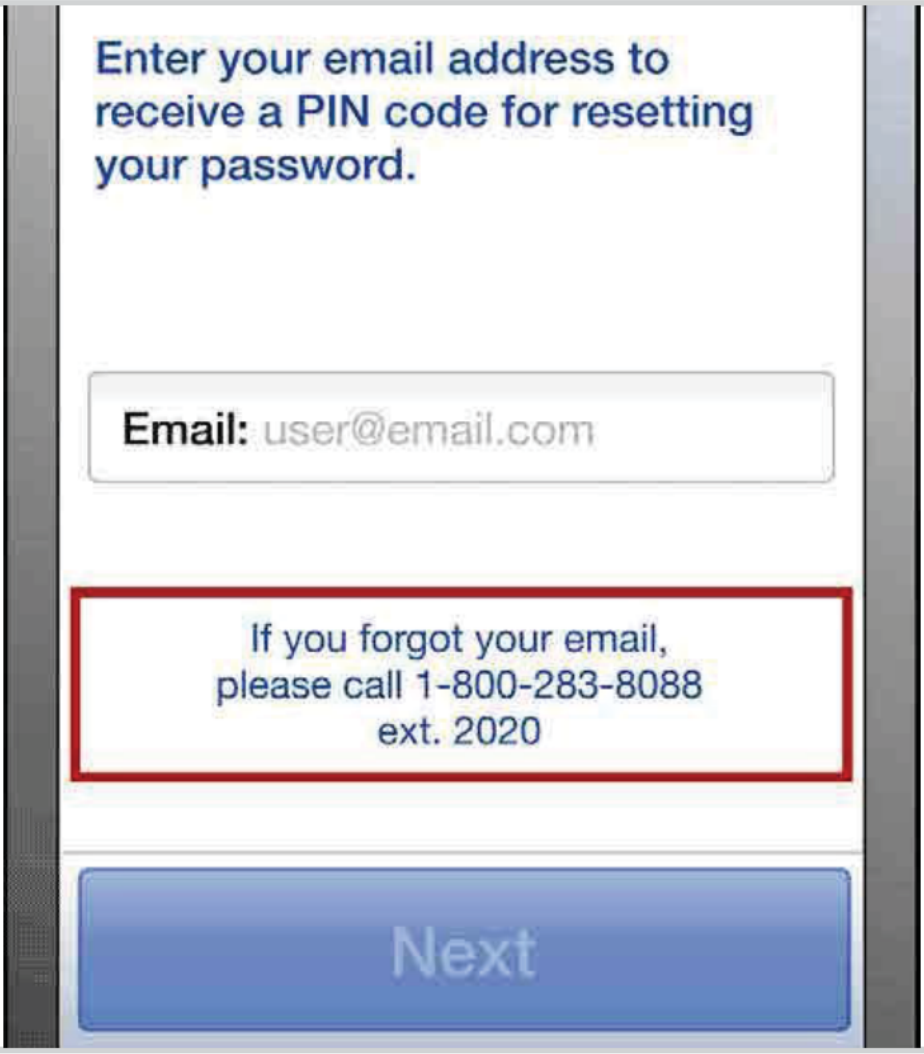


5. Tap the Reset password button. The Notification window will appear.

6. Tap the OK button. The Log in screen will appear.

Reference ID: 3991333

Start Session
Retrieve an Email Address



Call the EMD Serono patient support phone number to retrieve your email address.

Add Injection Data

Reference ID: 3991333

Add Injection Data
Introduction

⚠ CAUTION:

Read the Instructions for Use that comes with your Rebif® autoinjector. Be sure to check all injection details on the autoinjector's label (i.e., expiration date, dose, medication) before using the autoinjector and administering the injection.

Reference ID: 3991333

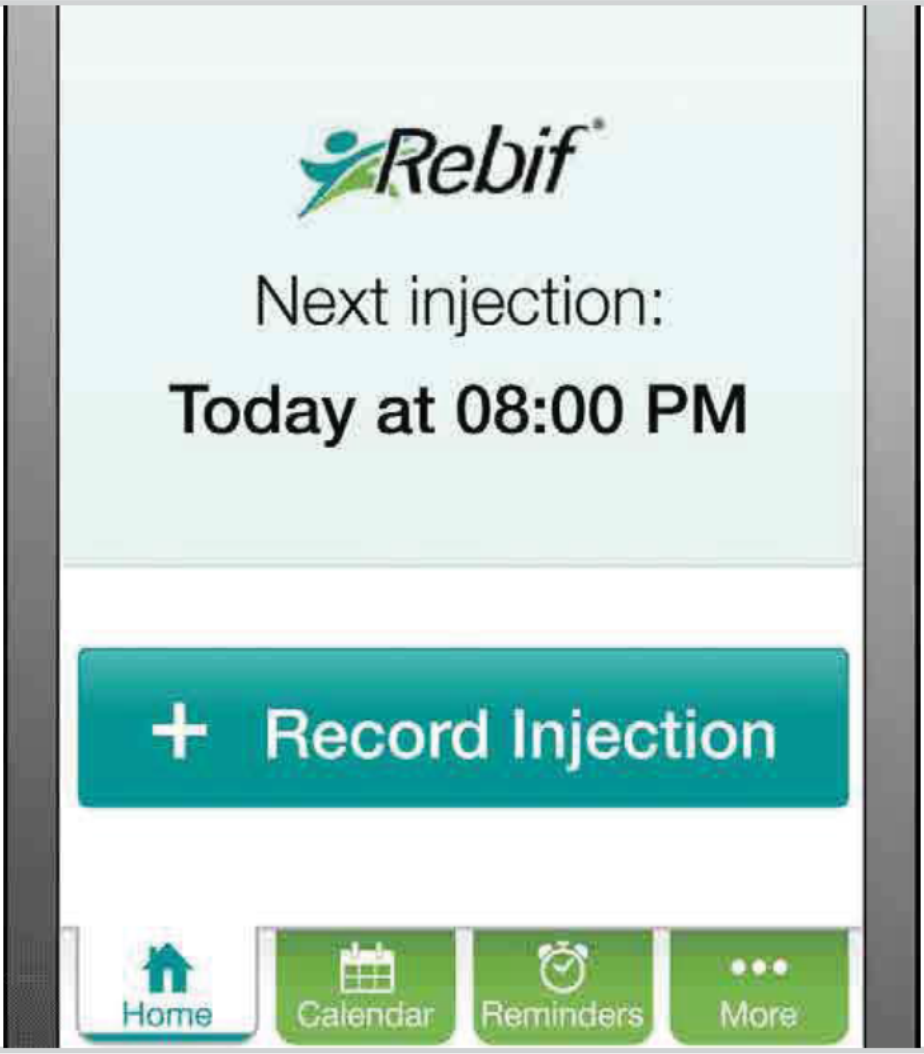
Add Injection Data Introduction

MSdialog™ Mobile Application offers you three ways to record your injections:

- Manually, by entering your injection details, OR
- Automatically, using a 2D code printed on the autoinjector's label, OR
- Automatically, using a near-field communication (NFC) tag in the autoinjector's label.

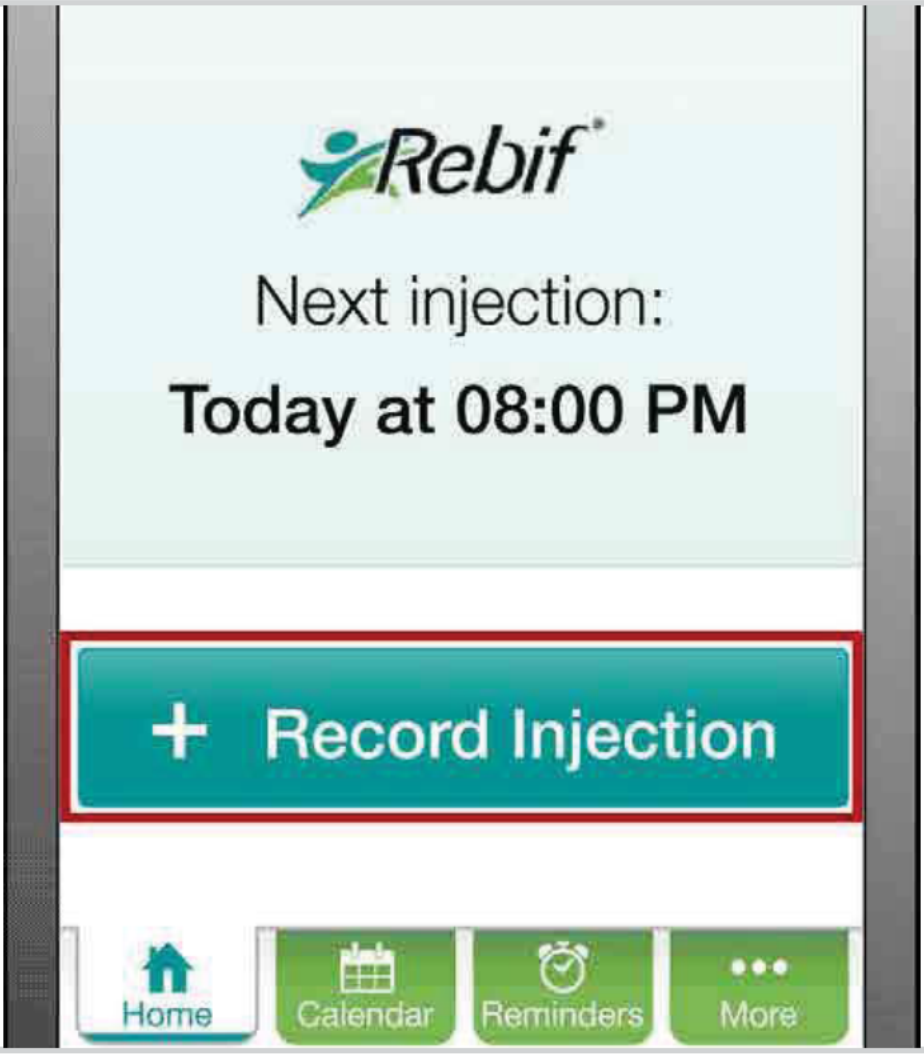
Reference ID: 3991333

Add Injection Data
Record Injection

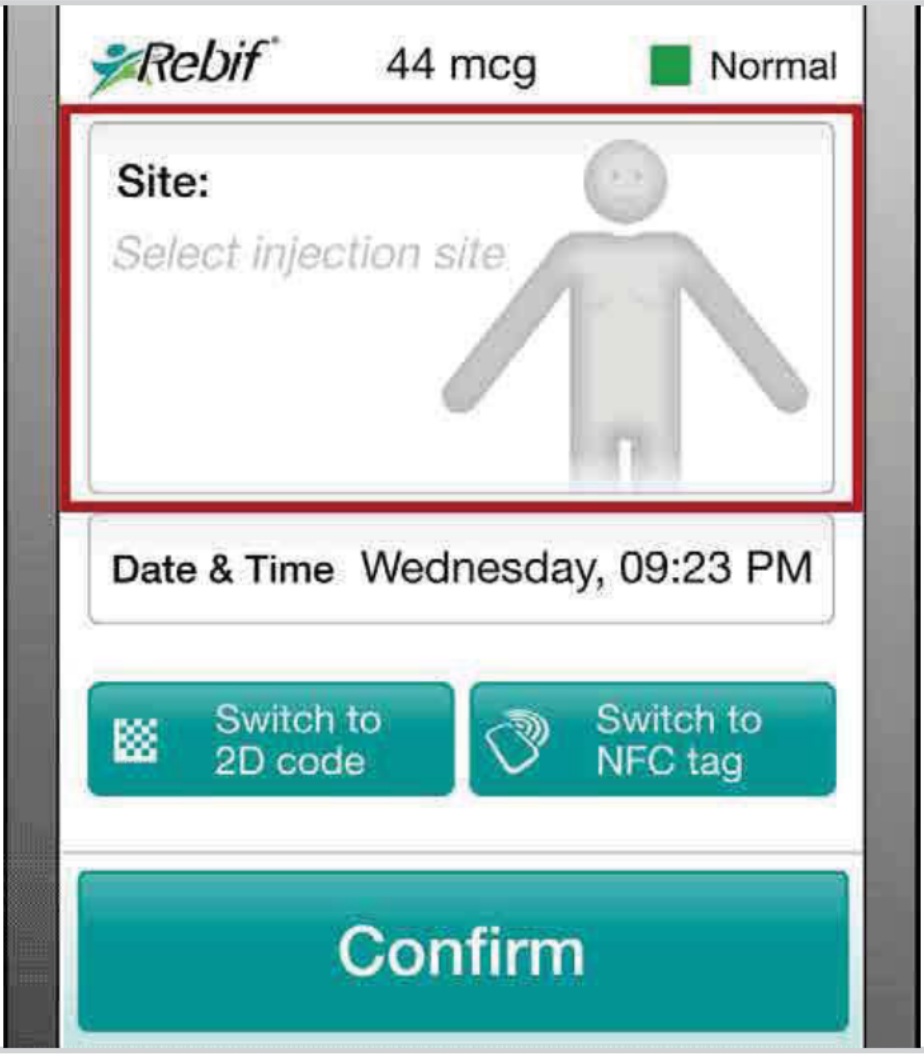


1. Log in to MSdialog™ Mobile Application. The Home screen will appear.

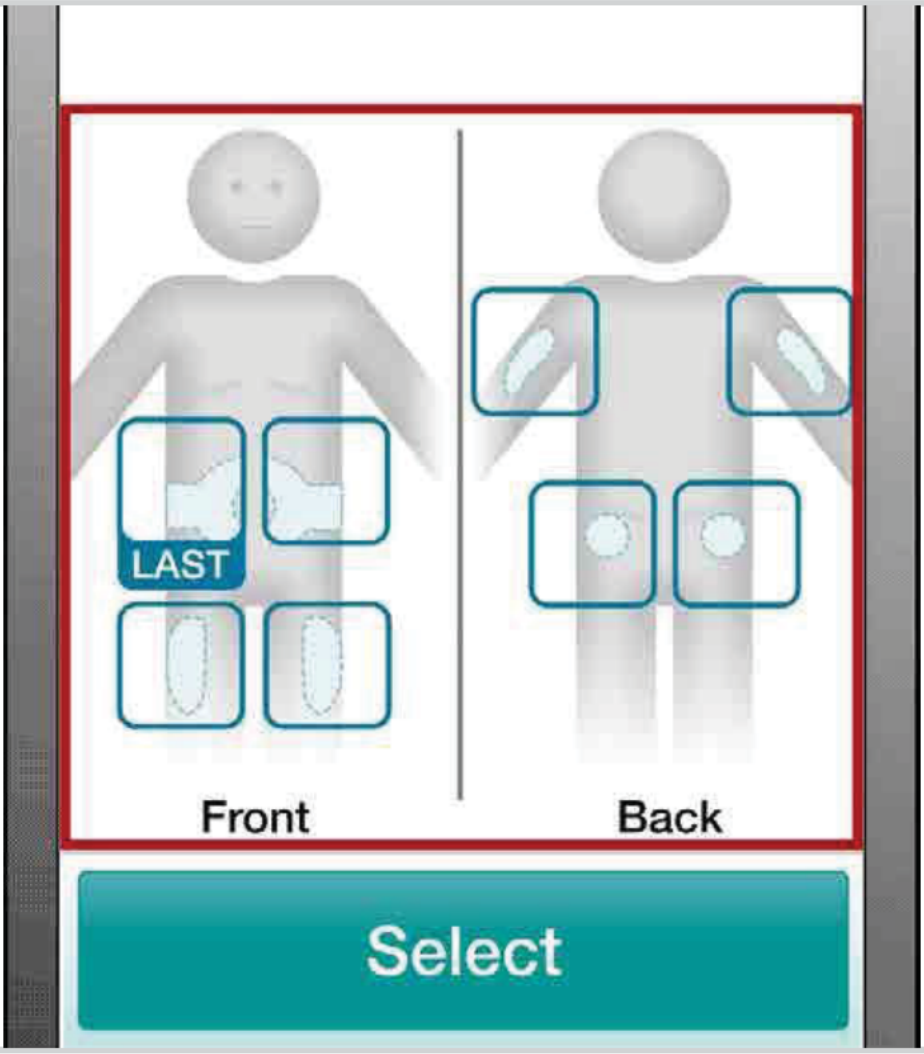
Reference ID: 3991333



2. Tap the Record Injection button to add an injection. The Record Injection screen will appear.

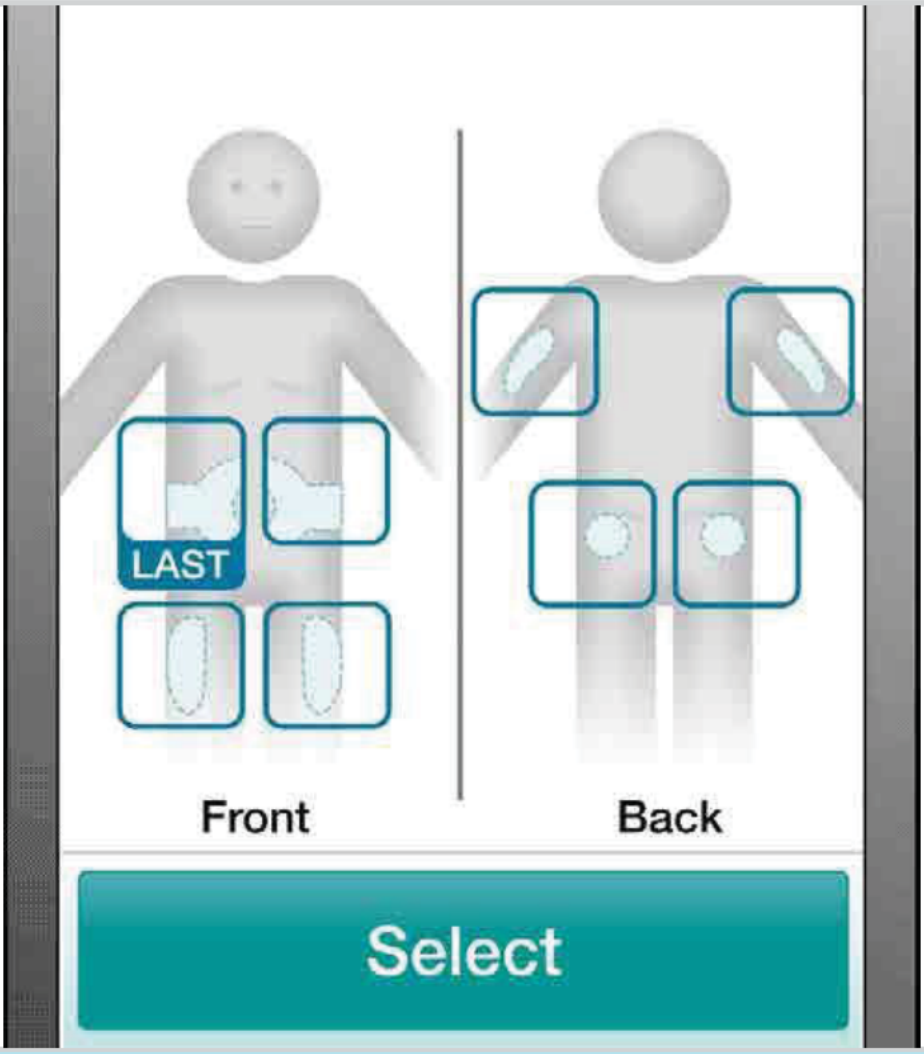


3. If you wish to record your injection site, tap the Site field to select the injection site on your body. The Select injection site screen will appear.



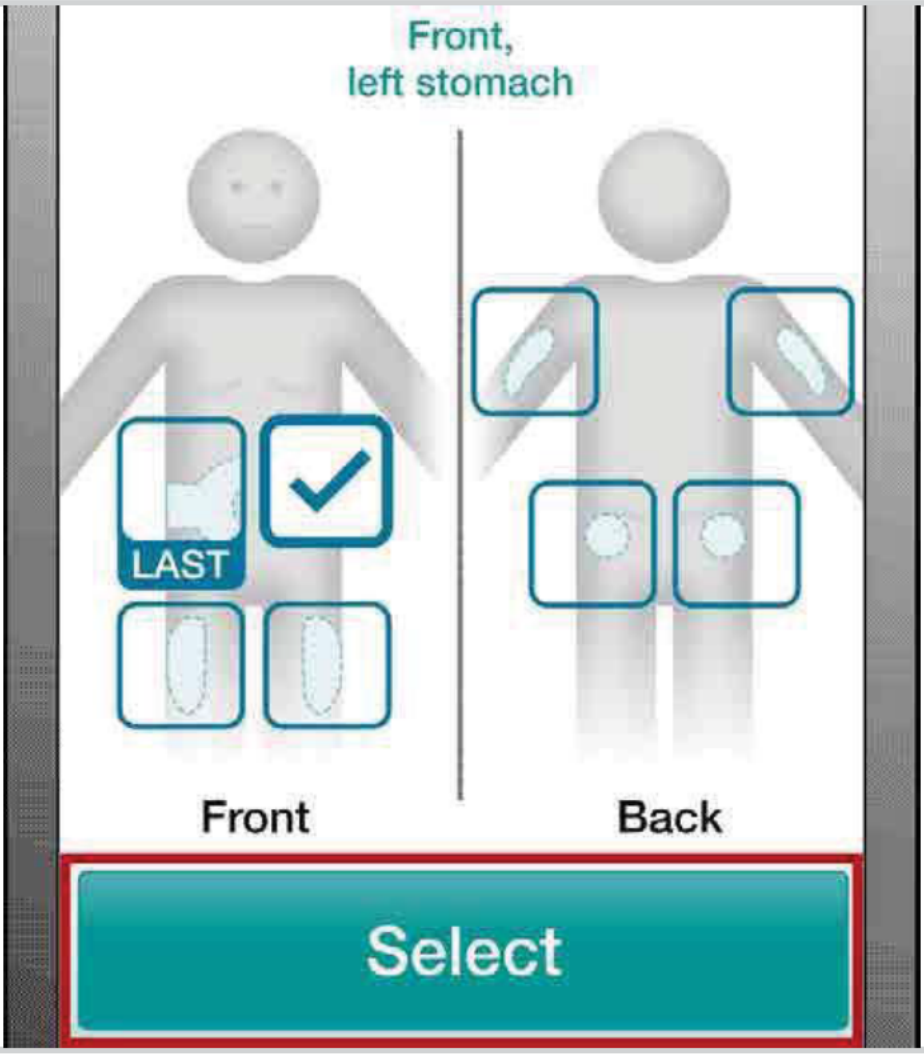
4. Tap one of the area buttons to select where the new injection will occur. The previous injection site is highlighted with the label: "LAST", if it was previously recorded.

Add Injection Data
Record Injection



NOTE:

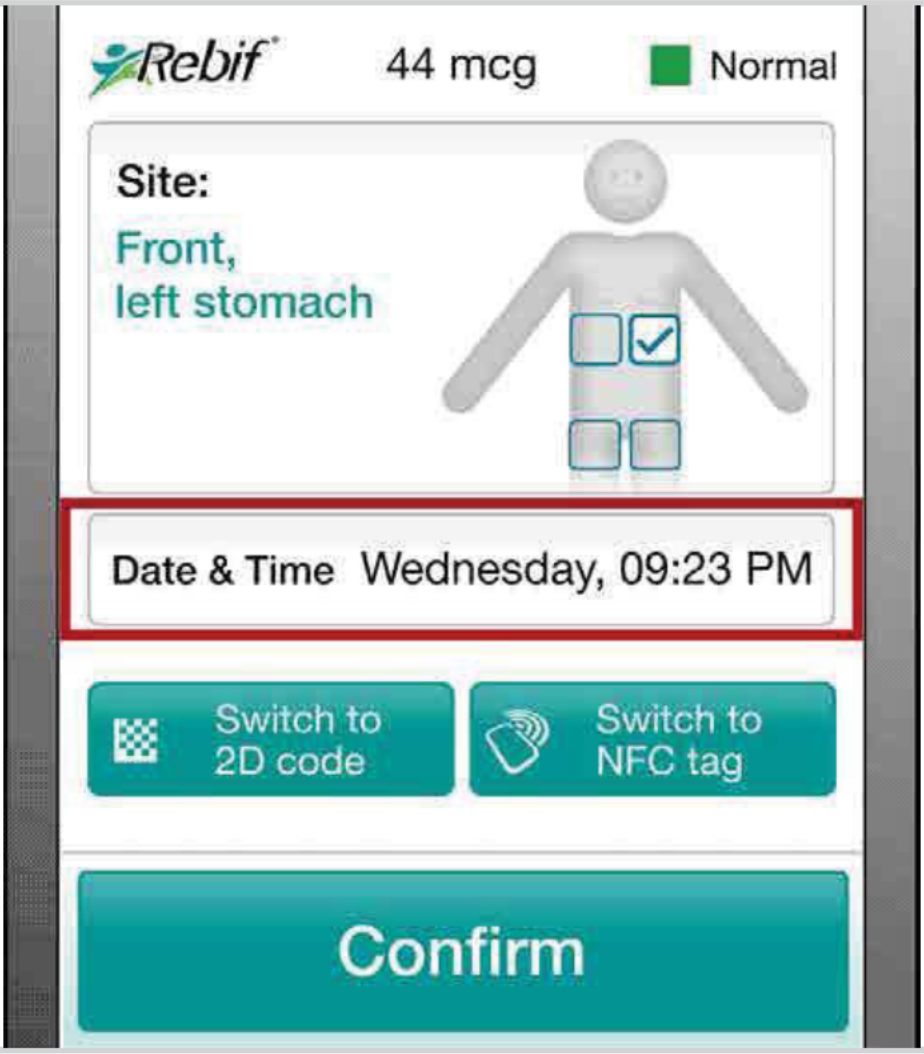
Select a different injection site from the injection site you last used.



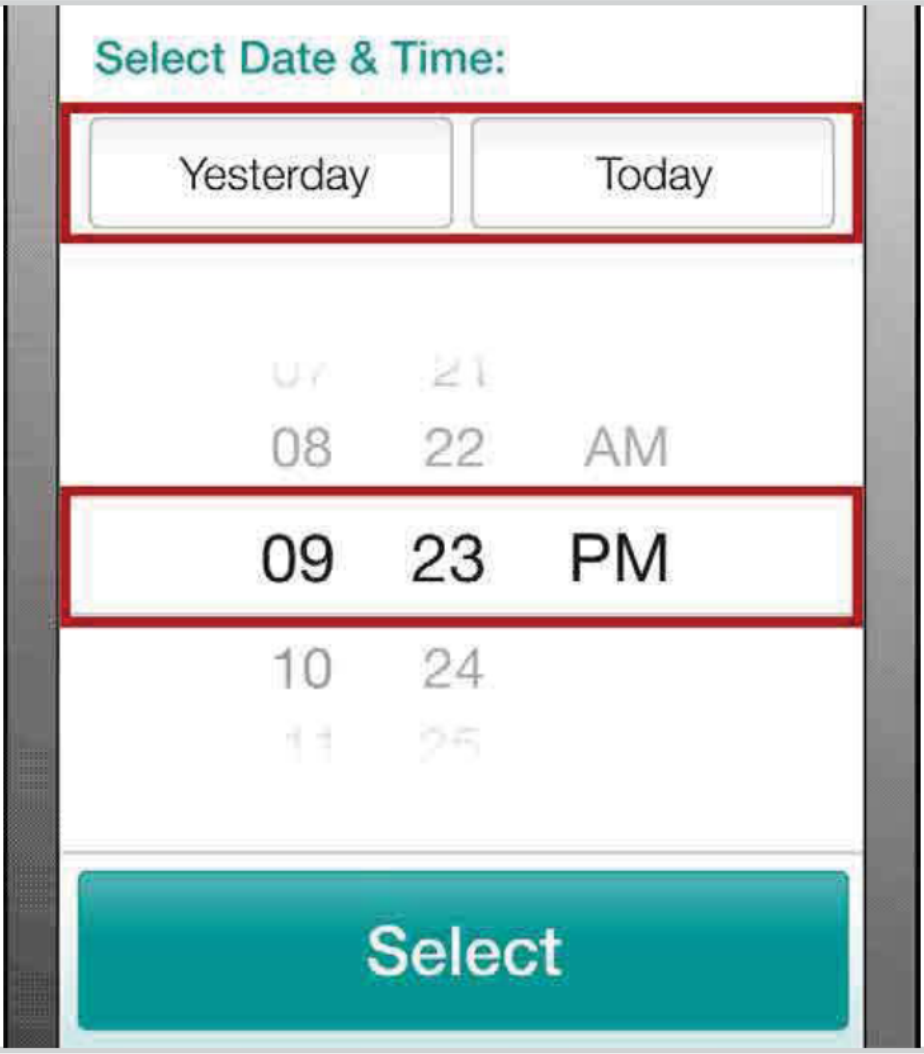
5. Tap the Select button. The Record Injection screen will appear showing your selected site.

Reference ID: 3991333

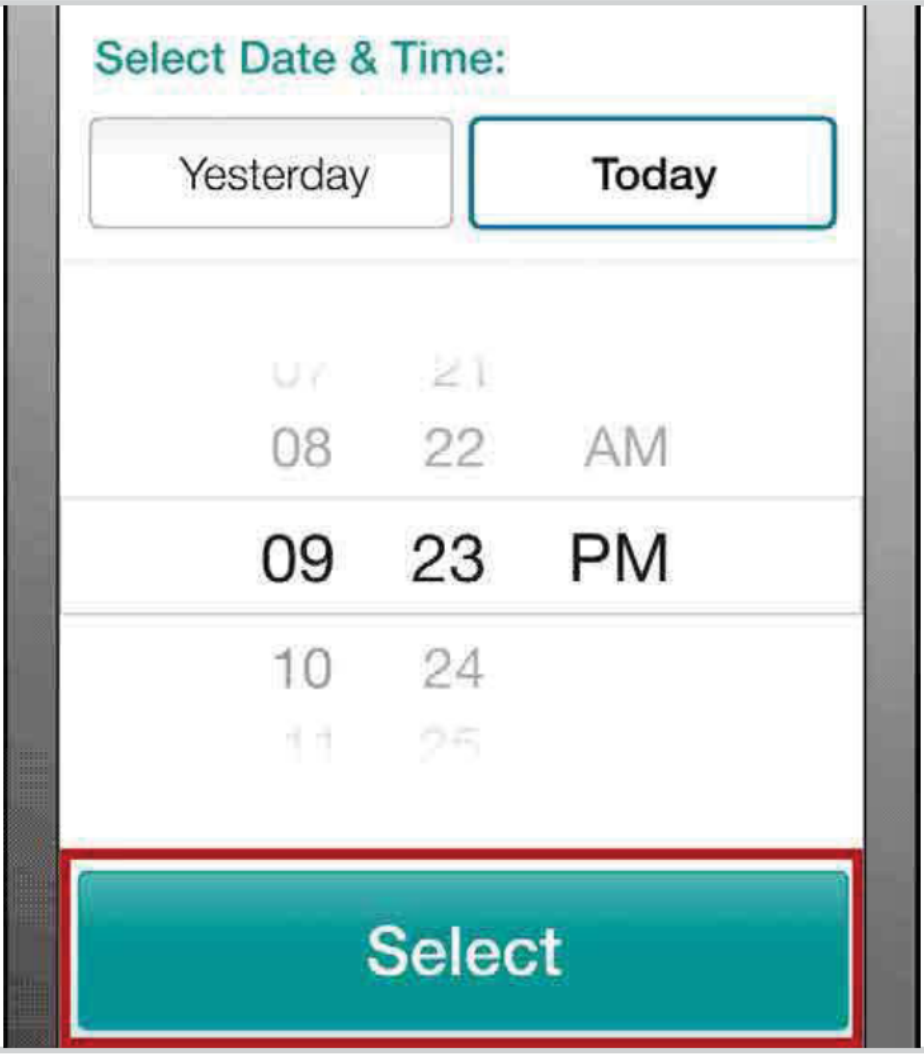
Add Injection Data
Record Injection



6. The Date **&** Time button appears pre-filled with the current information from your smartphone. If you wish to change the date and/or time, tap the Date **&** Time button.

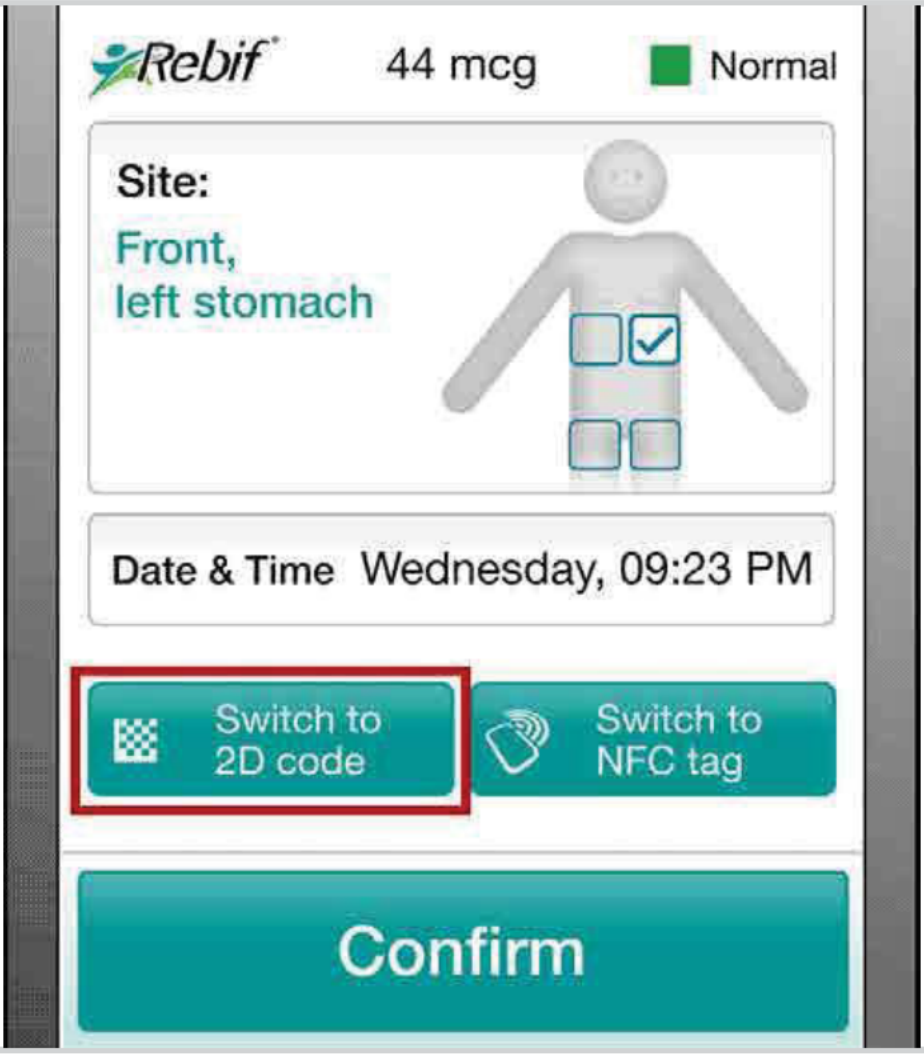


7. Select the Yesterday or Today button and set the timing for your new injection to take place.



8. Tap the Select button. The Record Injection screen will appear showing the selected options.

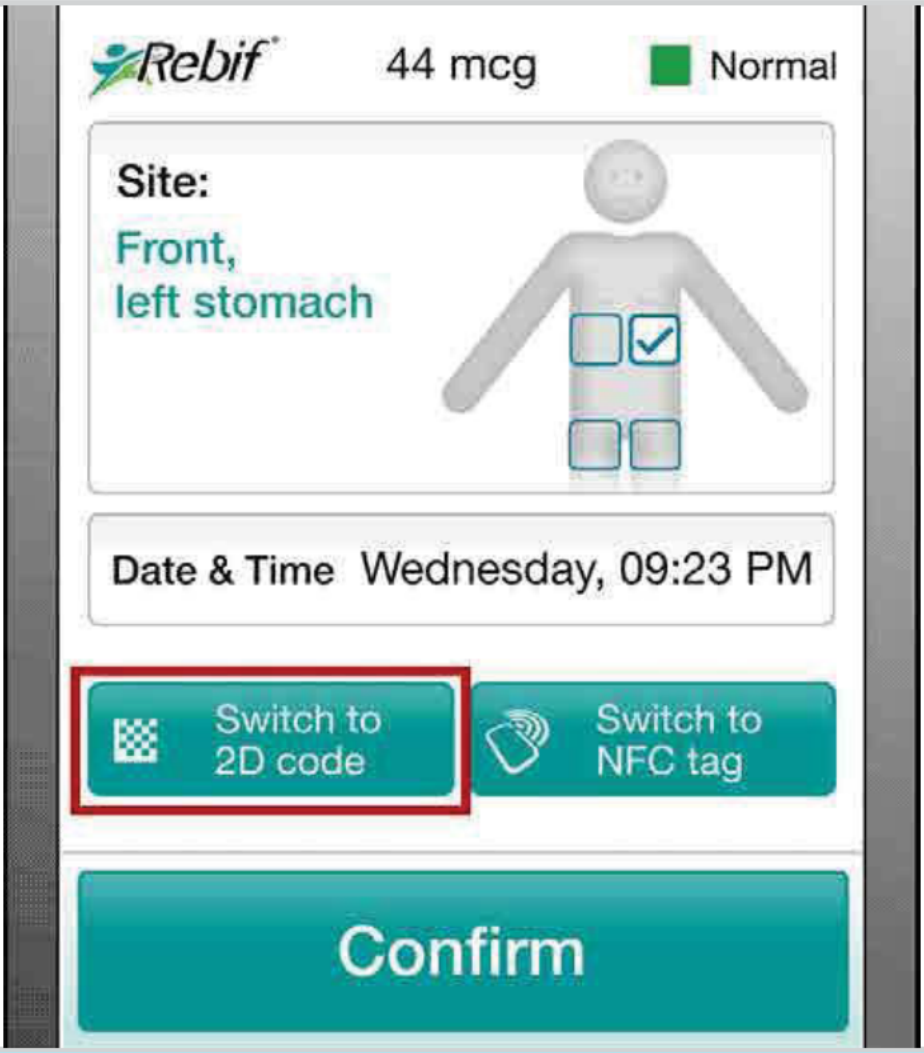
Add Injection Data
Add Details using 2D Code



1. Tap the Switch to 2D Code button. The smartphone's camera screen will appear.

Reference ID: 3991333

Add Injection Data
Add Details using 2D Code



NOTE:

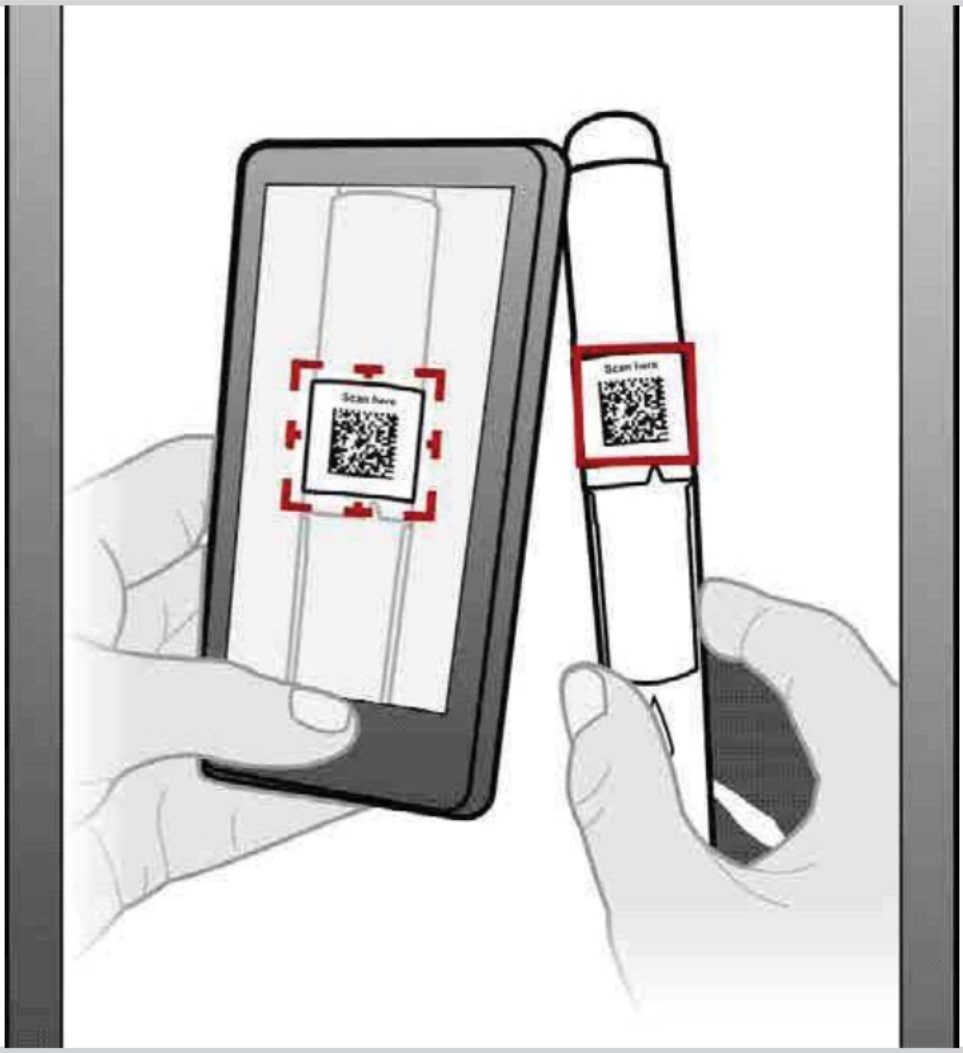
If you have an Android phone OS 4.1 that has a NFC enabled reader, you can also tap the Switch to NFC Tag button to add autoinjector details.

Reference ID: 3991333

Add Injection Data
Add Details using 2D Code

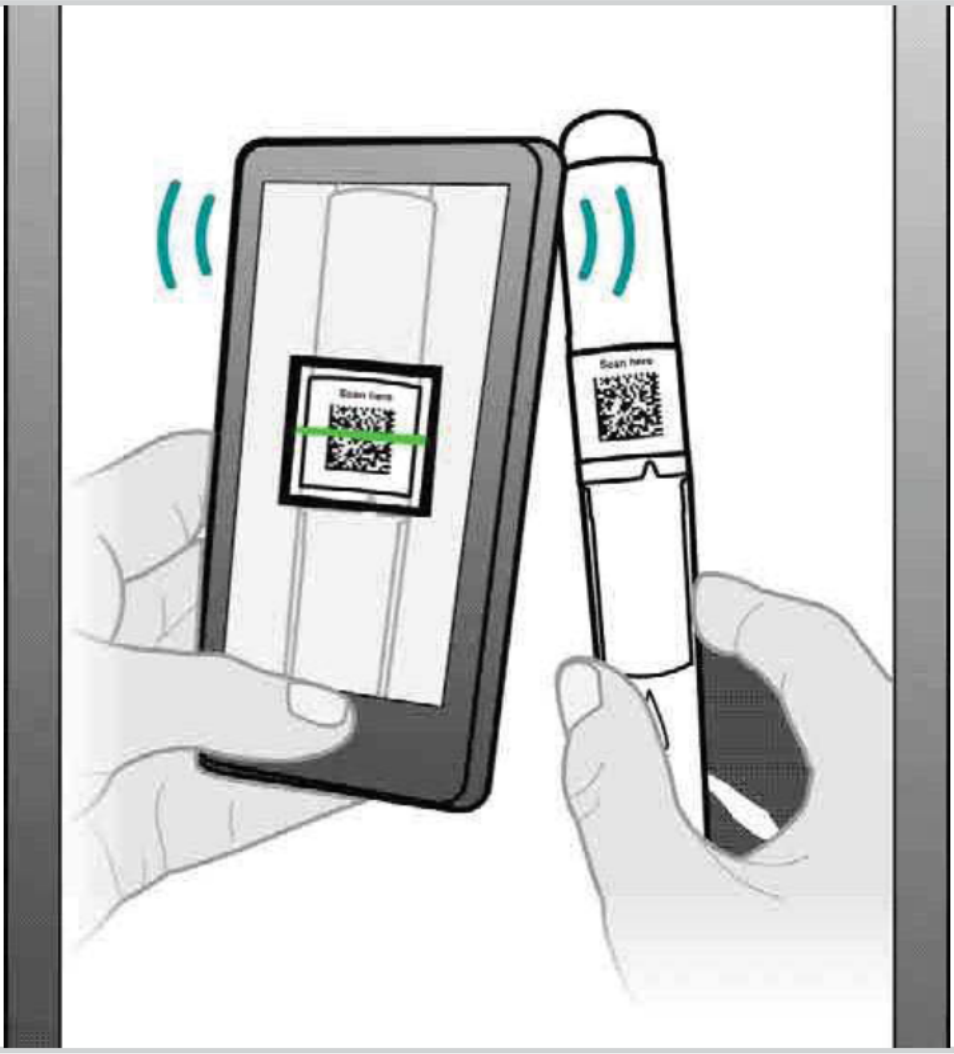
2. Find the 2D code on the autoinjector. The 2D code is a small, square, black barcode located to the left of the words “Rebif® Rebidose” on the autoinjector’s label.

Reference ID: 3991333



3. Aim the smartphone's camera at the autoinjector's 2D code, centering the 2D code in the camera's view.

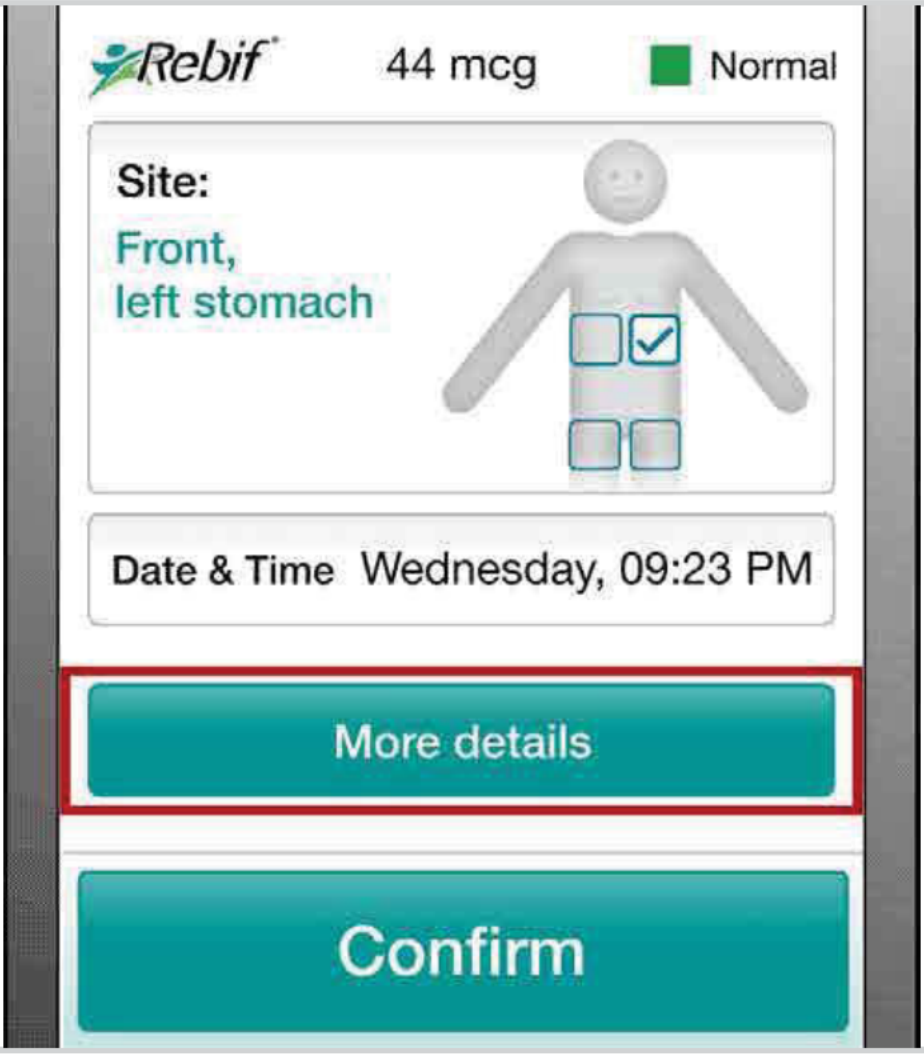
Reference ID: 3991333



4. Hold the smartphone steady until it makes a sound and/or vibrates, and shows a notification on the screen, indicating that the 2D code has been scanned. The Record Injection screen will appear.

Reference ID: 3991333

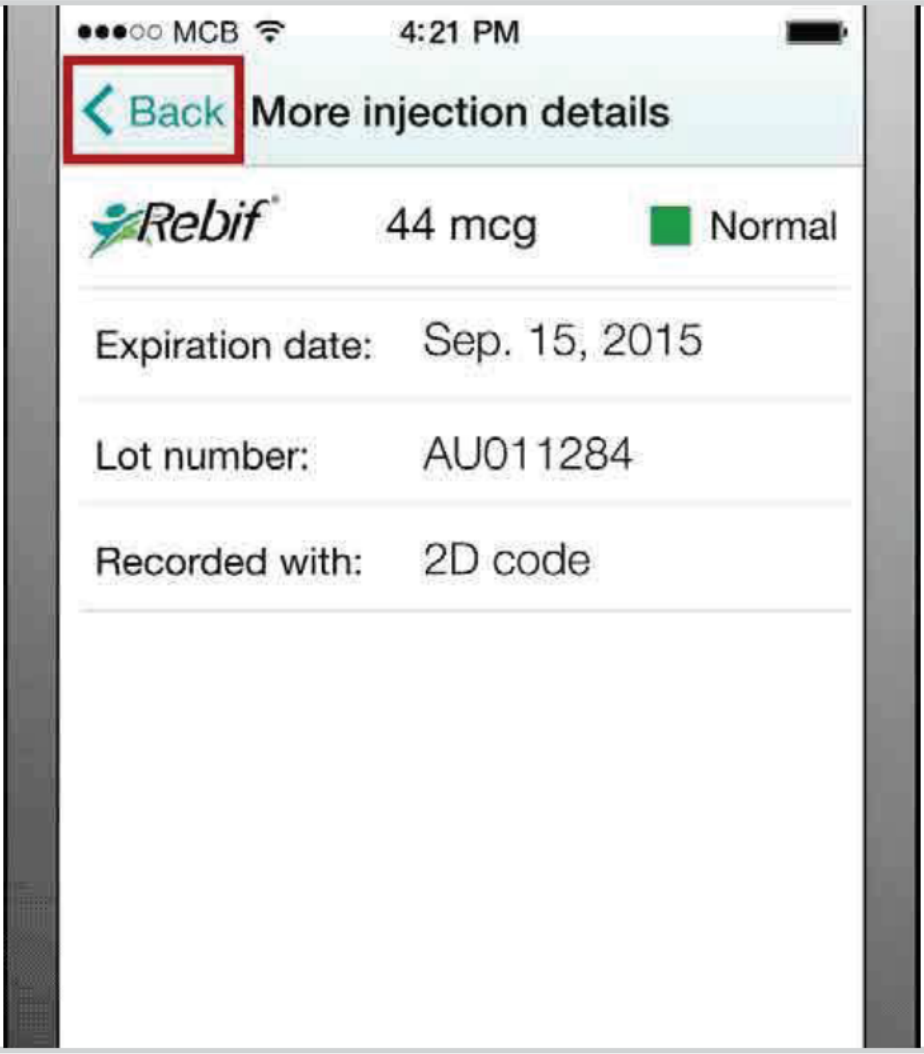
Add Injection Data
Add Details using 2D Code



5. Tap the More details button to review the injection details and confirm they match the information on the autoinjector's label.

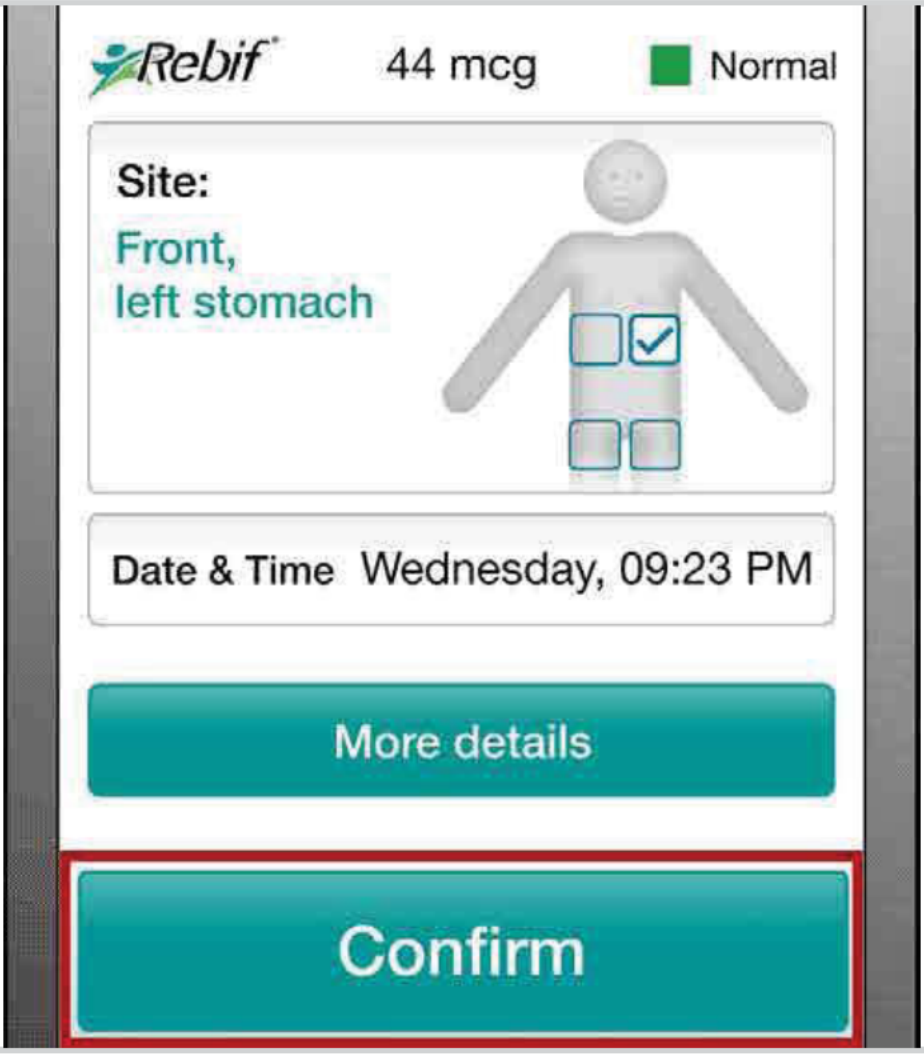
Reference ID: 3991333

Add Injection Data
Add Details using 2D Code



6. Tap Back. The Record Injection screen will appear.

Add Injection Data
Add Details using 2D Code



7. Tap the Confirm button. The Notification window will appear indicating that an injection has been added.

Reference ID: 3991333

8. Tap the OK button. The Home screen will appear showing your new scheduled injection.

Reference ID: 3991333

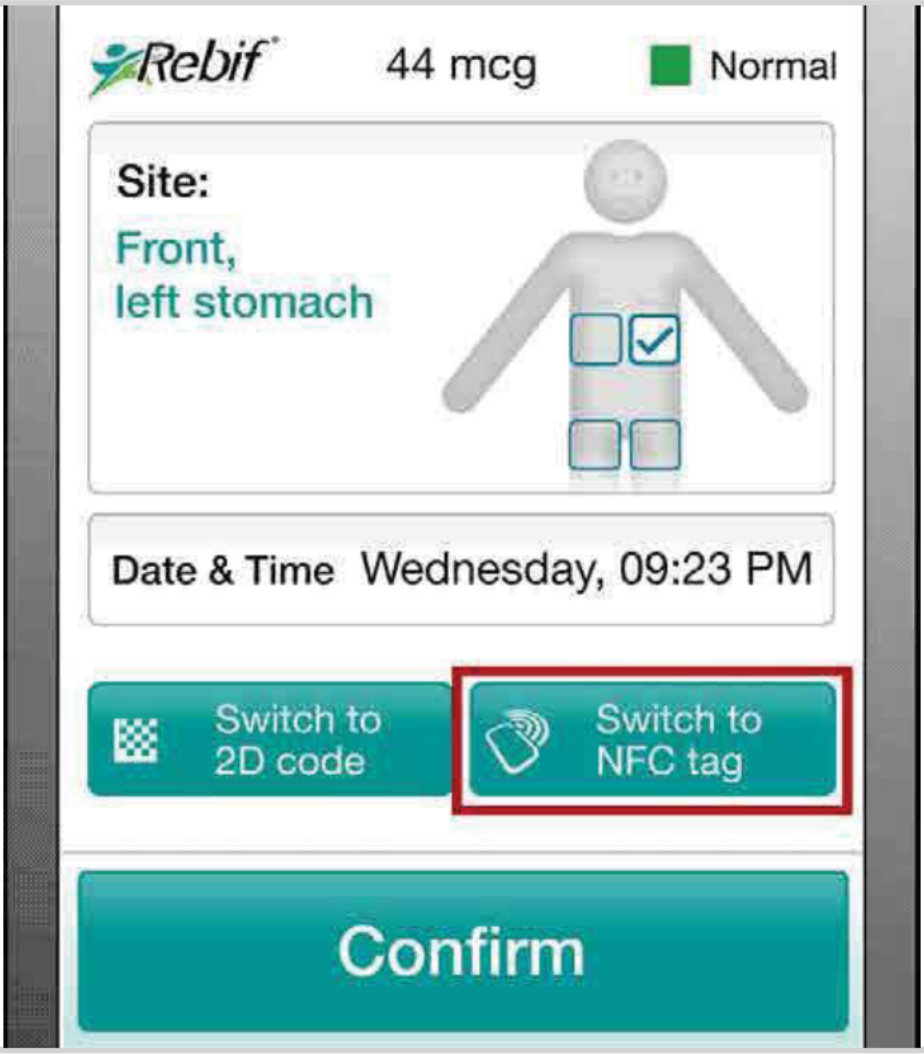
Add Injection Data
Add Details using NFC Tag

The near-field communication (NFC) tag is a small chip in the autoinjector's label, which can be read by some smartphones.

> NOTE:
> The NFC tag can only be read by Android phones with NFC reader functionality, featuring OS 4.1 and up. Check your smartphone's manual for references to NFC reader availability.

Reference ID: 3991333

Add Injection Data
Add Details using NFC Tag



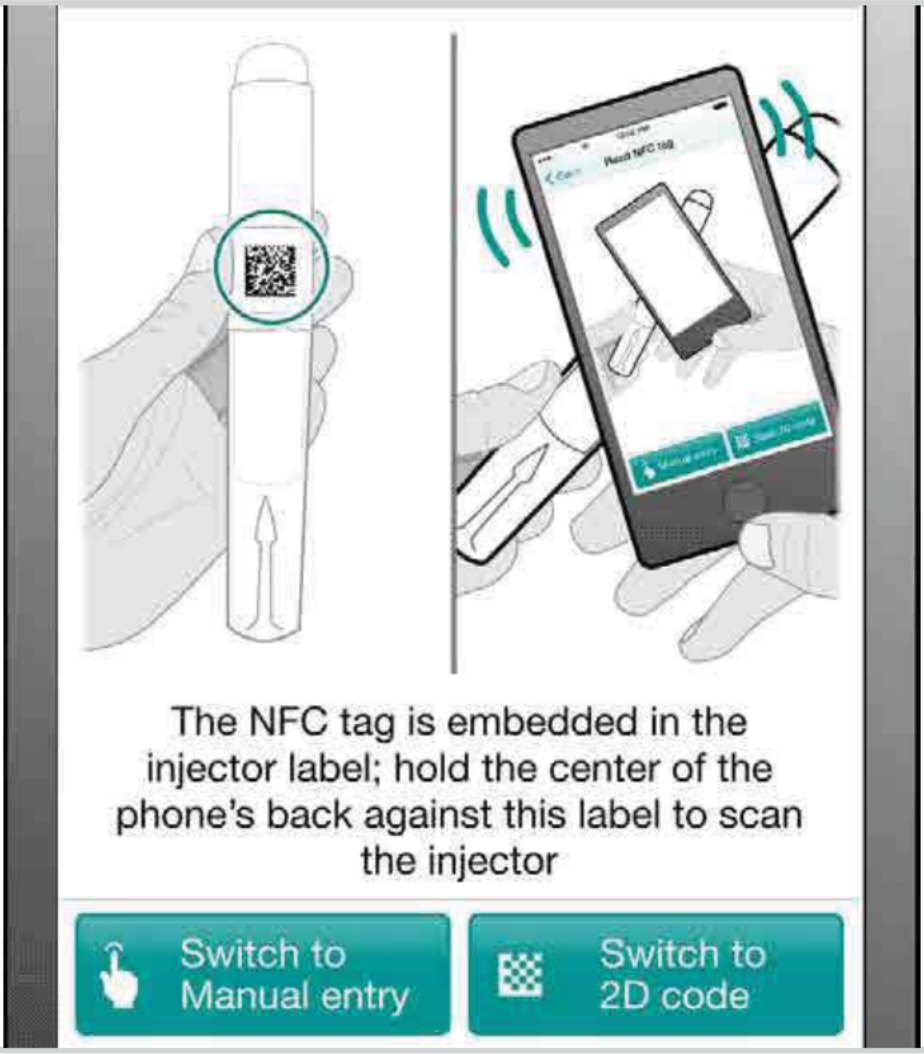
1. Tap the Switch to NFC Tag button. The NFC instruction screen will appear.

Reference ID: 3991333

Add Injection Data
Add Details using NFC Tag

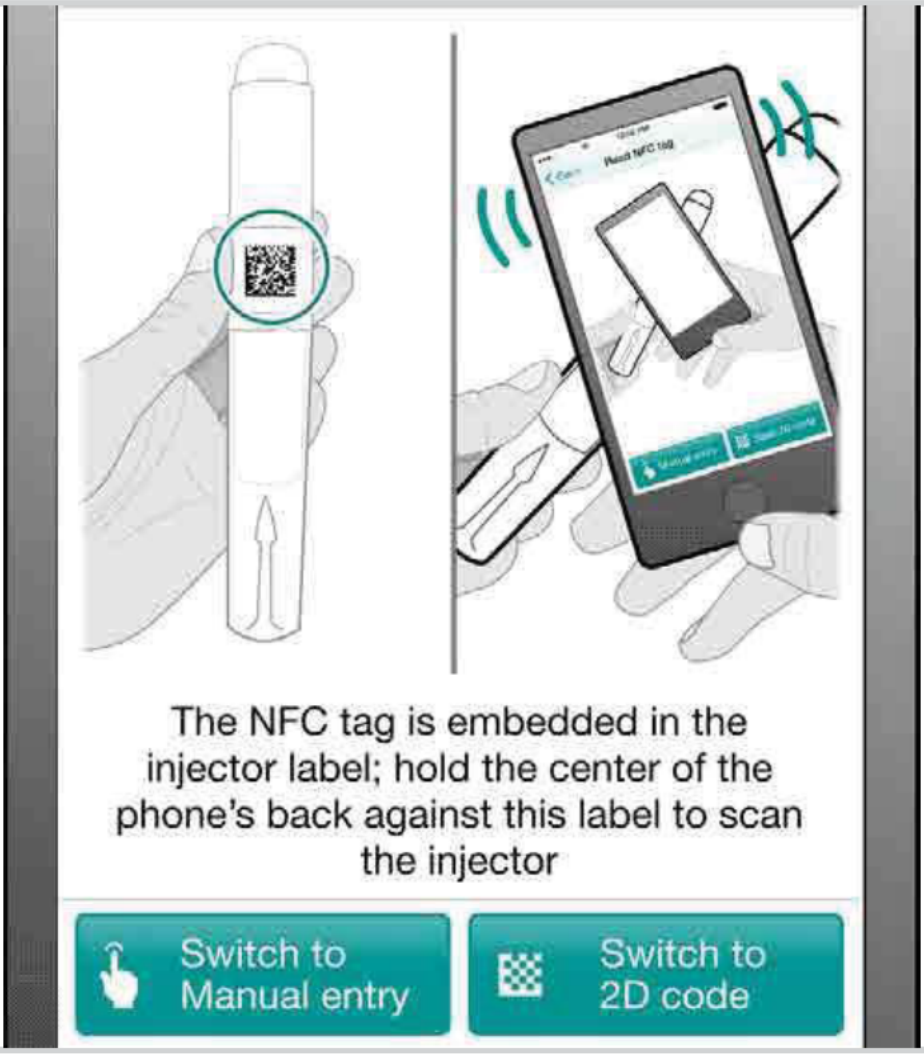
2. Look for the square barcode symbol shown on the autoinjector. The NFC tag is embedded underneath this symbol on the label.

Reference ID: 3991333



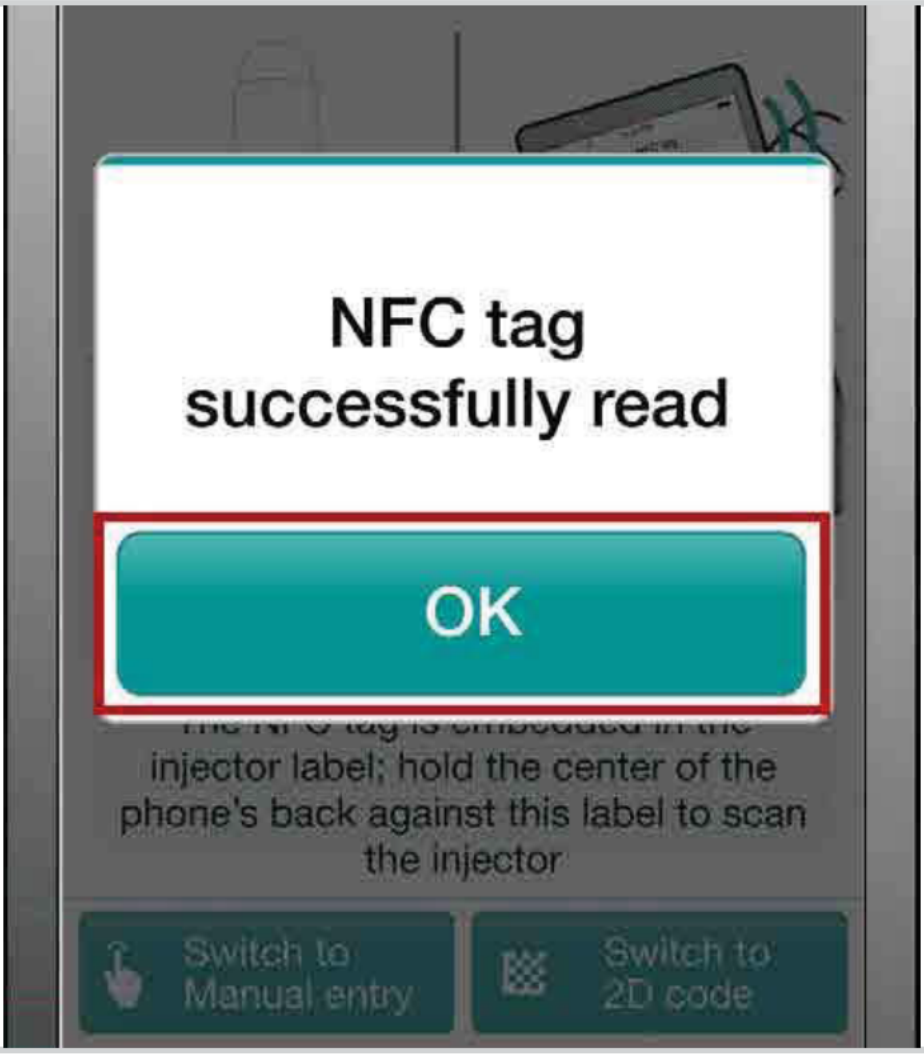
3. Hold the NFC tag against the back of the smartphone, making sure the label contacts the smartphone's back. Hold the smartphone steady until it makes a sound and/or vibrates, and shows a notification on the

Add Injection Data
Add Details using NFC Tag



screen indicating that the NFC tag has been read. The Notification window will appear, indicating that the injection details have been added.

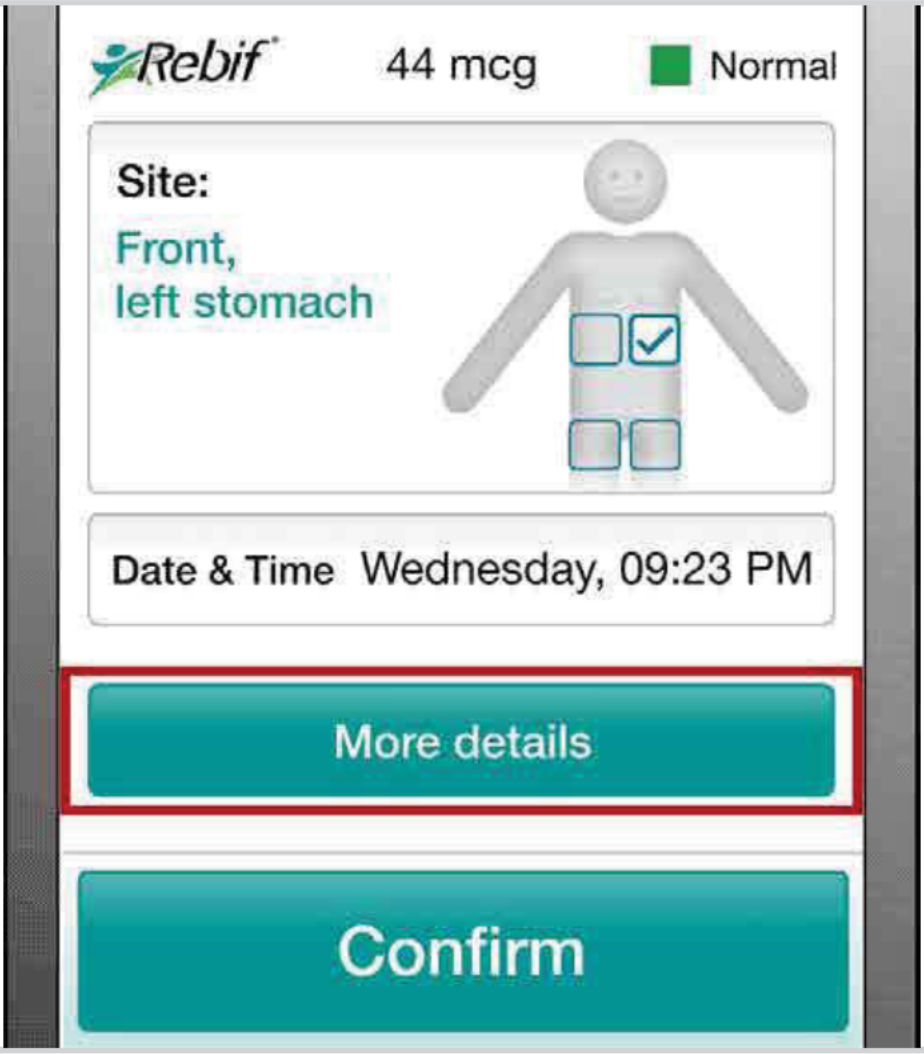
Reference ID: 3991333



4. Tap the OK button. The Record Injection screen will appear.

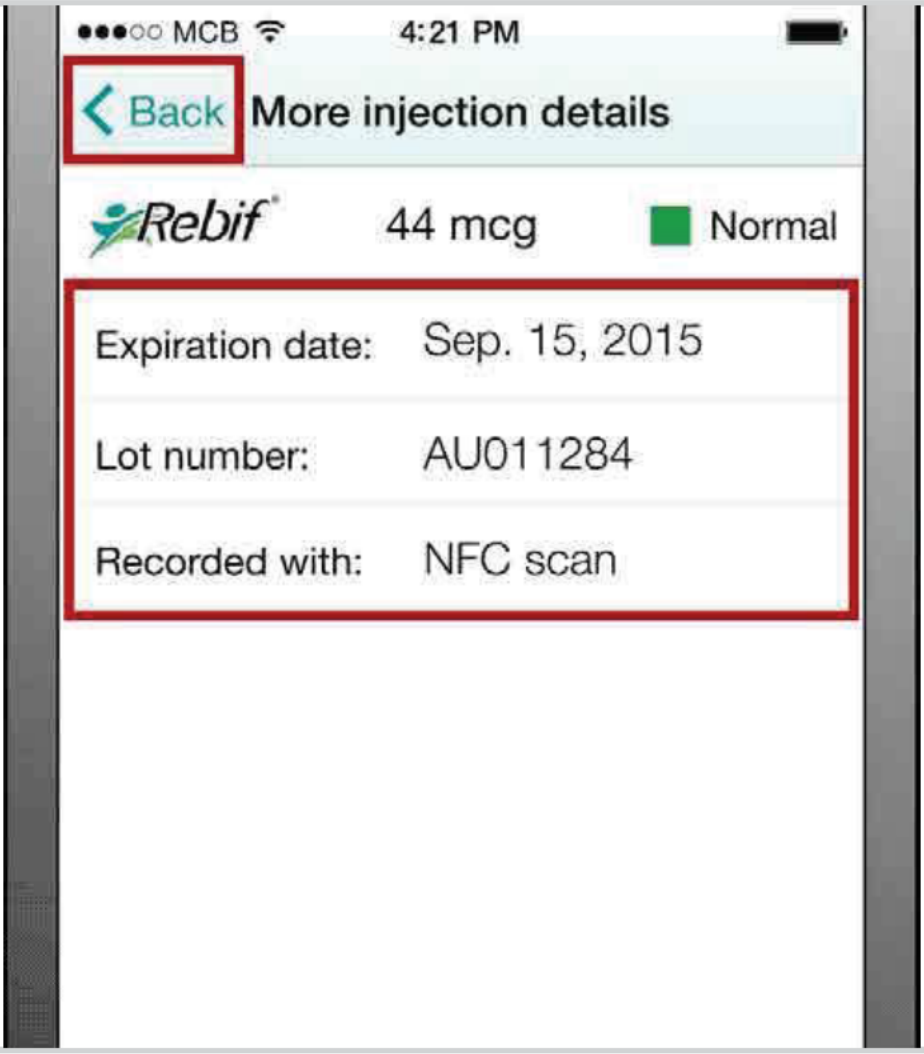
Reference ID: 3991333

Add Injection Data
Add Details using NFC Tag



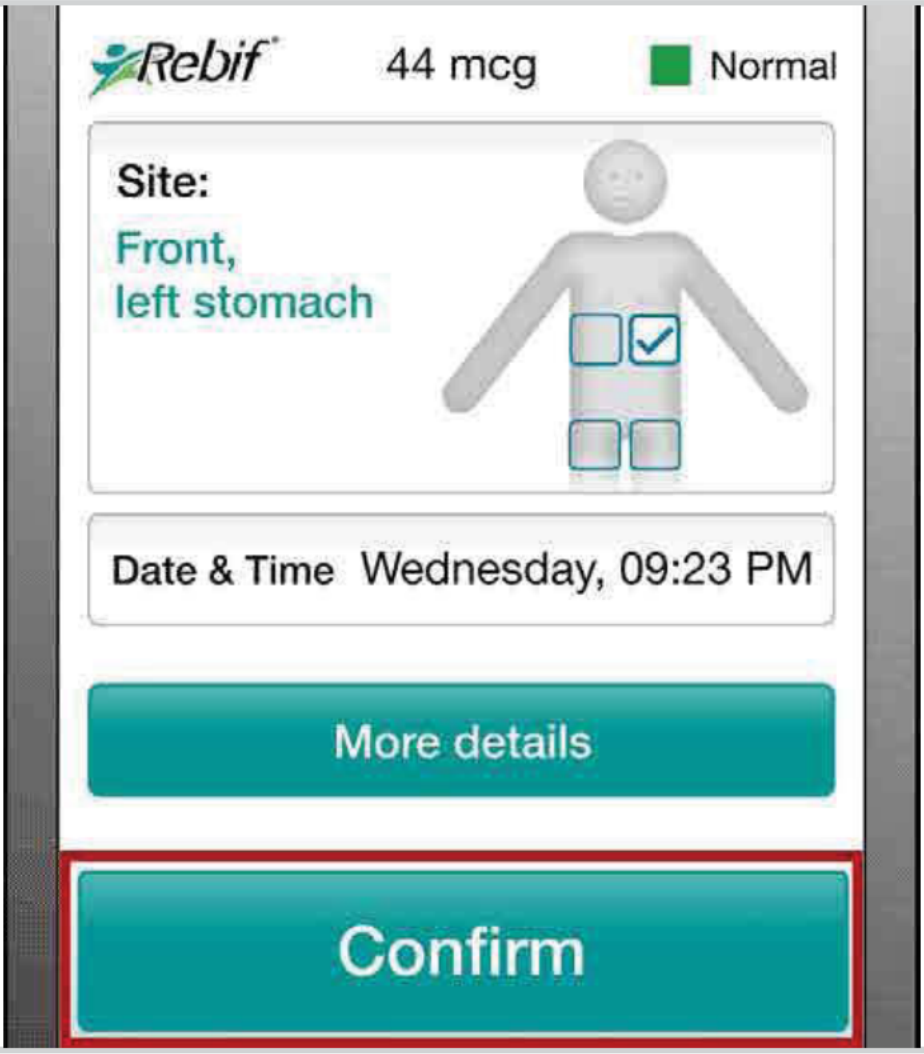
5. You may also tap the More details button to review the injection details.

Add Injection Data
Add Details using NFC Tag



6. Review the injection details to confirm they match the information on the autoinjector's label. Tap the Back button to return to the Record Injection screen.

Reference ID: 3991333



7. Tap the Confirm button. The Notification window will appear indicating that an injection has been added.

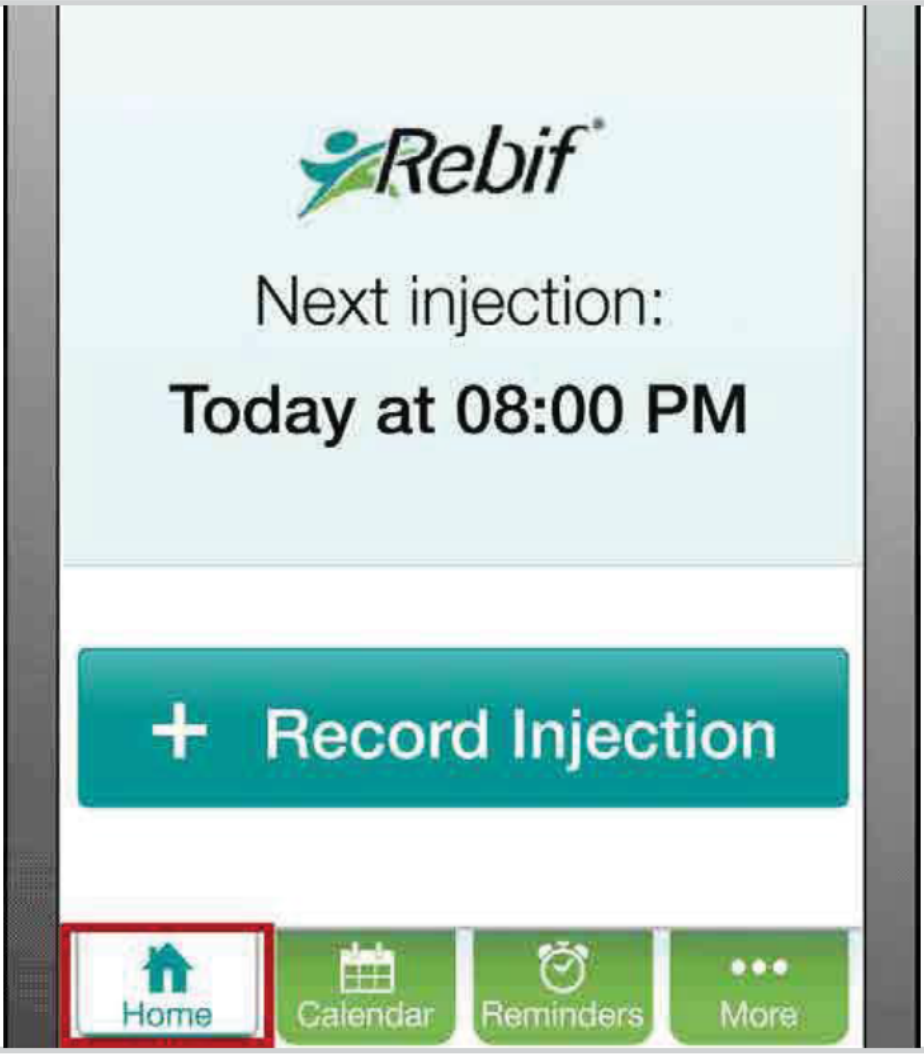
8. Tap the OK button. The Home screen will appear showing your new scheduled injection.

Reference ID: 3991333

Home Tab

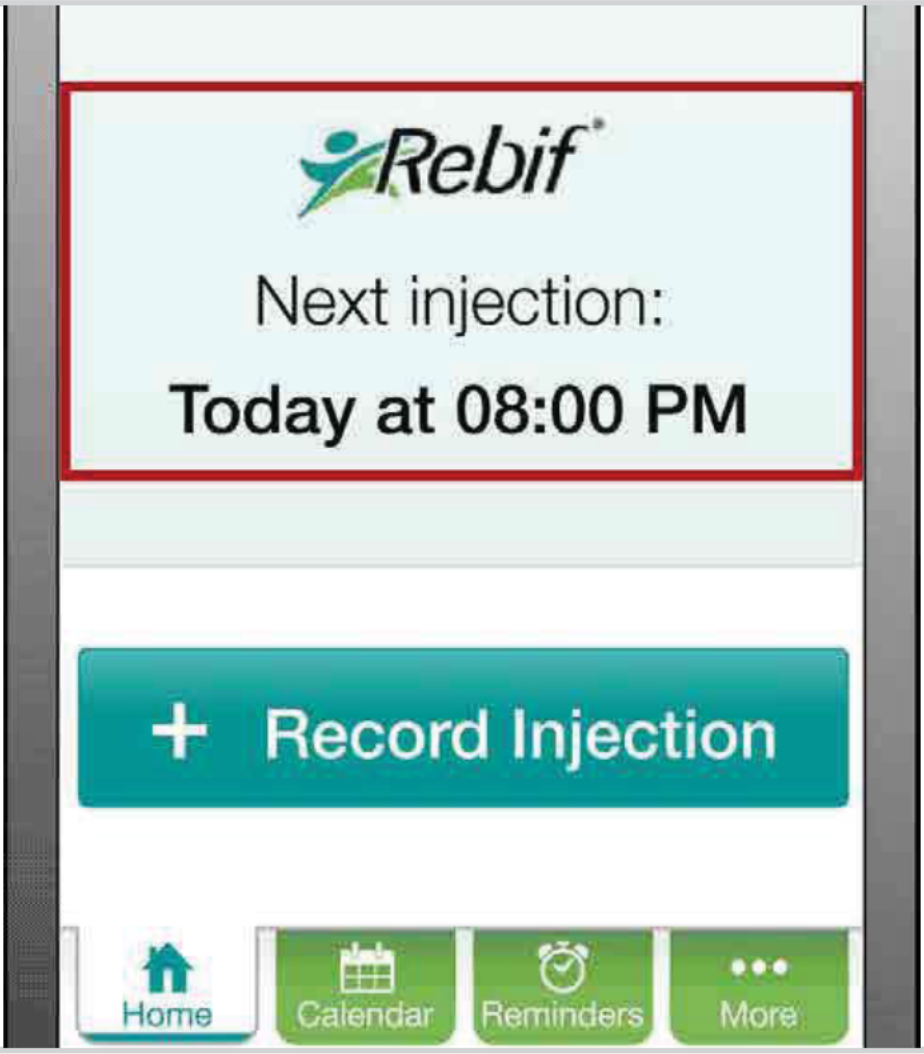
Reference ID: 3991333

Home Tab
About the Home Tab



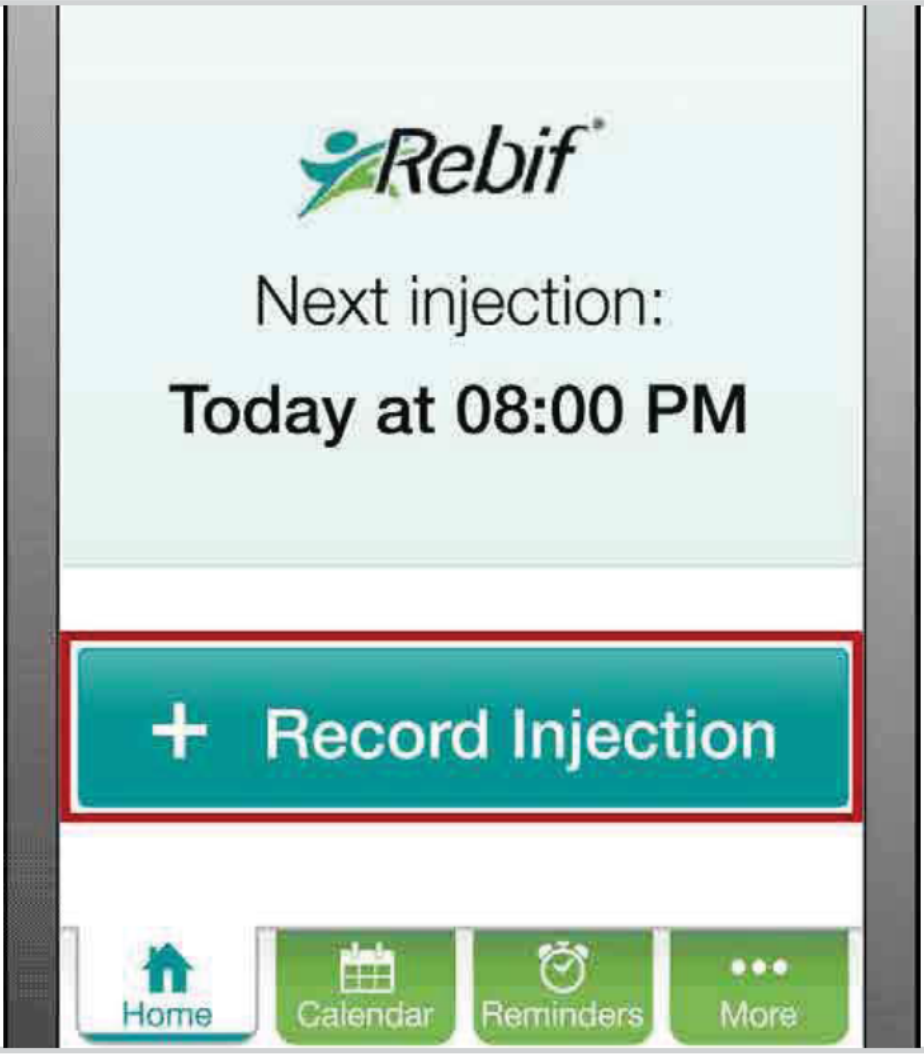
You can access the Home screen by tapping the Home tab. The Home screen is the first screen that appears after you log in.

Home Tab
View Next Injection



The top of the Home screen shows your medication name and the next scheduled injection information.

Home Tab
Record Injection



To record an injection, tap the Record injection button.

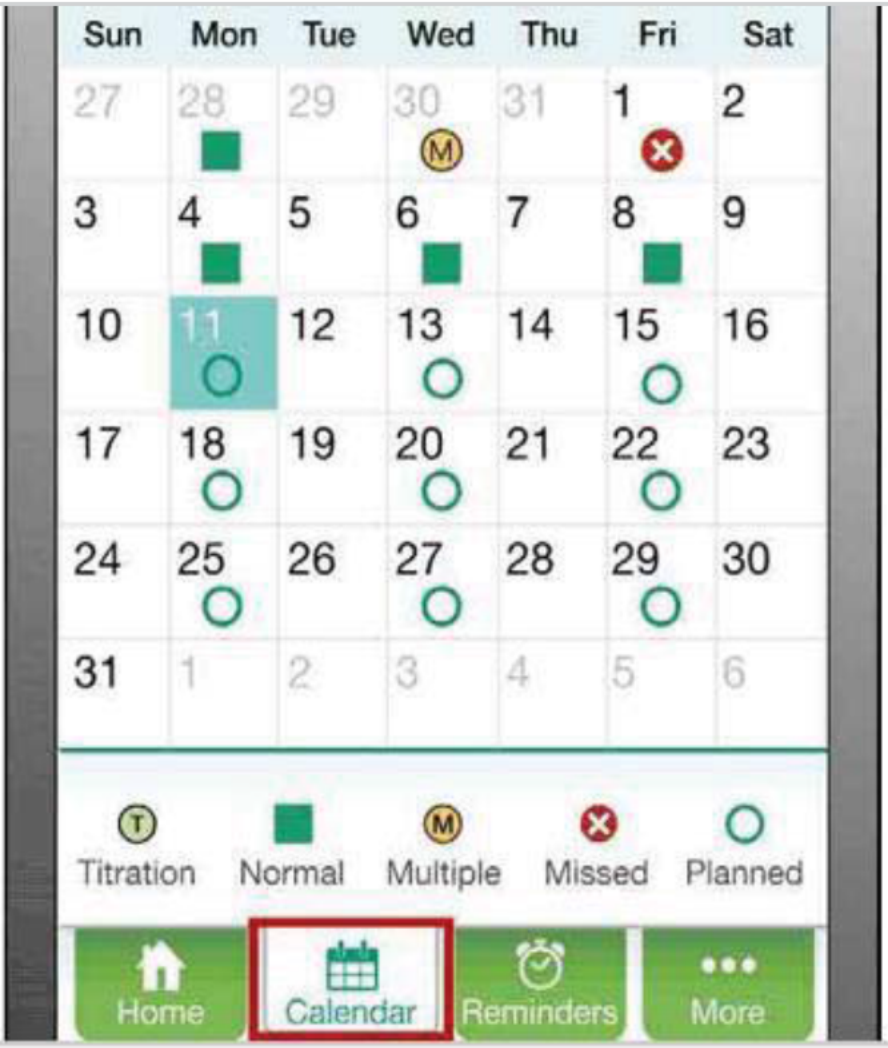
See "Add Injection Data" for more information about recording an injection.

Reference ID: 3991333

Calendar Tab

Reference ID: 3991333

Calendar Tab
About the Calendar



You can access the Calendar screen by tapping the Calendar button on the Home screen.

Calendar Tab
About the Calendar

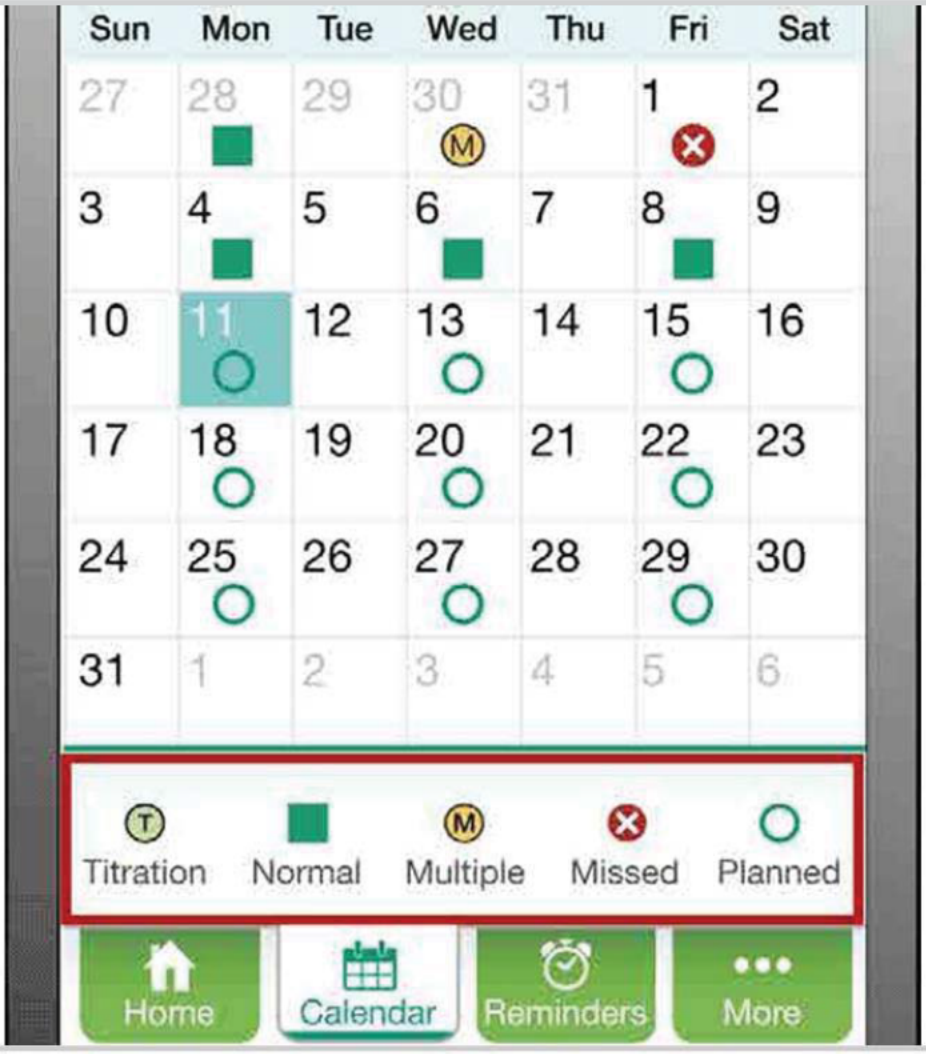
On the Calendar screen you can:

- Select different months to display by tapping the next or previous month.

Calendar Tab
About the Calendar

- Review injection details by tapping the day of the event.

Calendar Tab
Injection Status

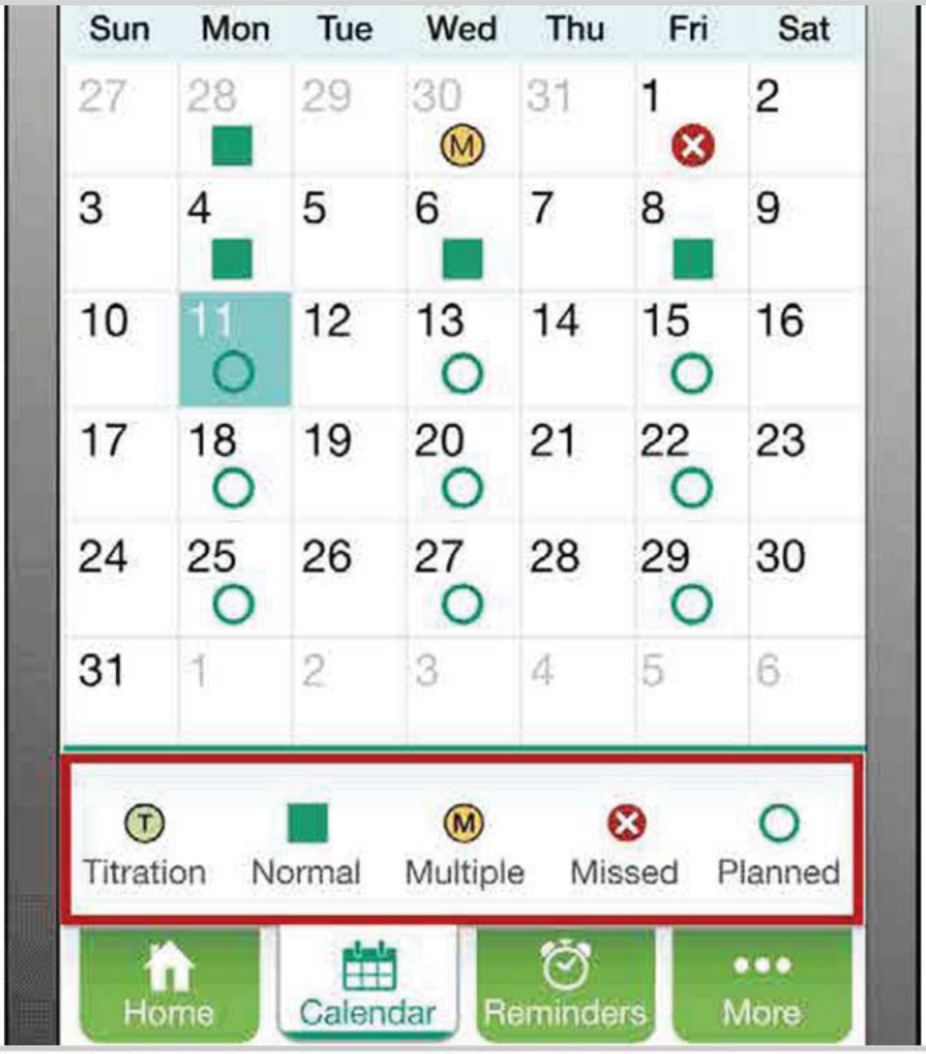


The Calendar screen indicates the status of past and future injections. The status of an injection is indicated by the icon that appears on the calendar:

- Titration: A sequence of injections with gradually increasing medication dose until the prescribed final dosage is reached.
- Normal: A single daily injection.
- Multiple: Two or more injections on the same day.
- Missed: If you missed an injection.
- Planned: Scheduled injections.

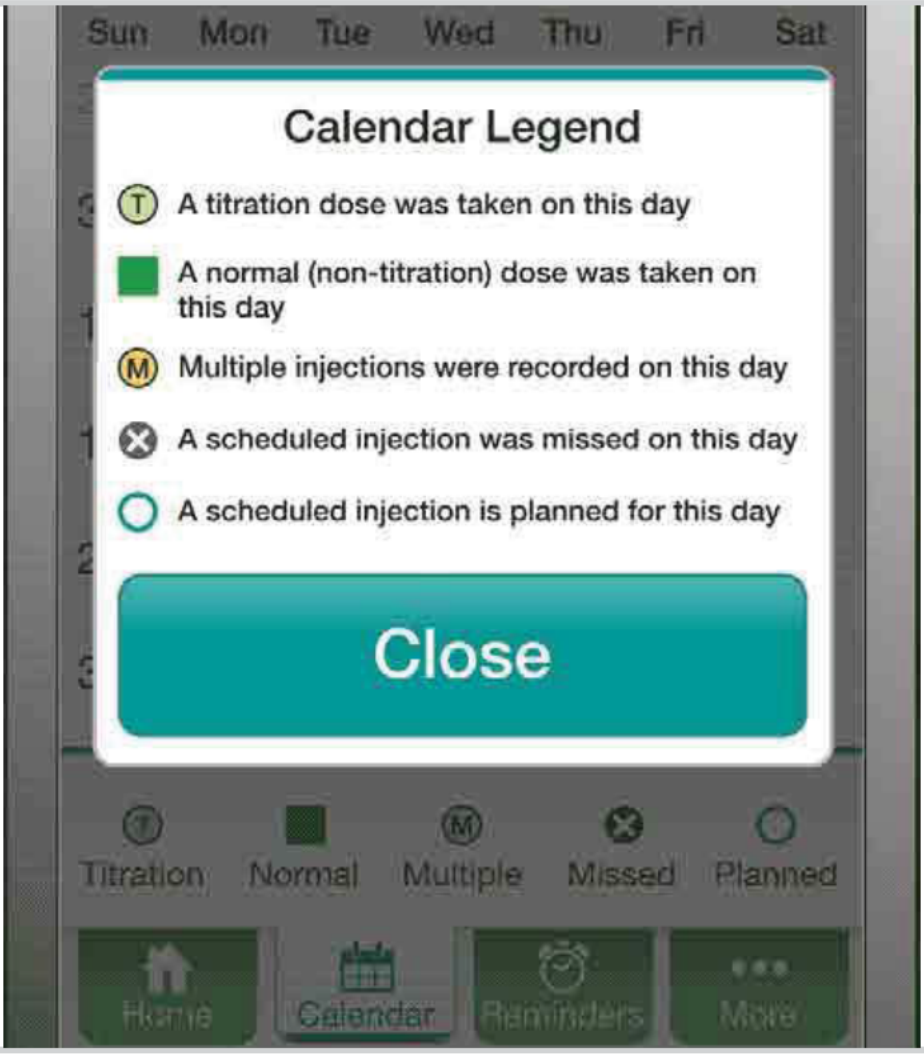
Reference ID: 3991333

Calendar Tab
Injection Status



You can access the legend of the icons by tapping on the icons.

Calendar Tab
Injection Status

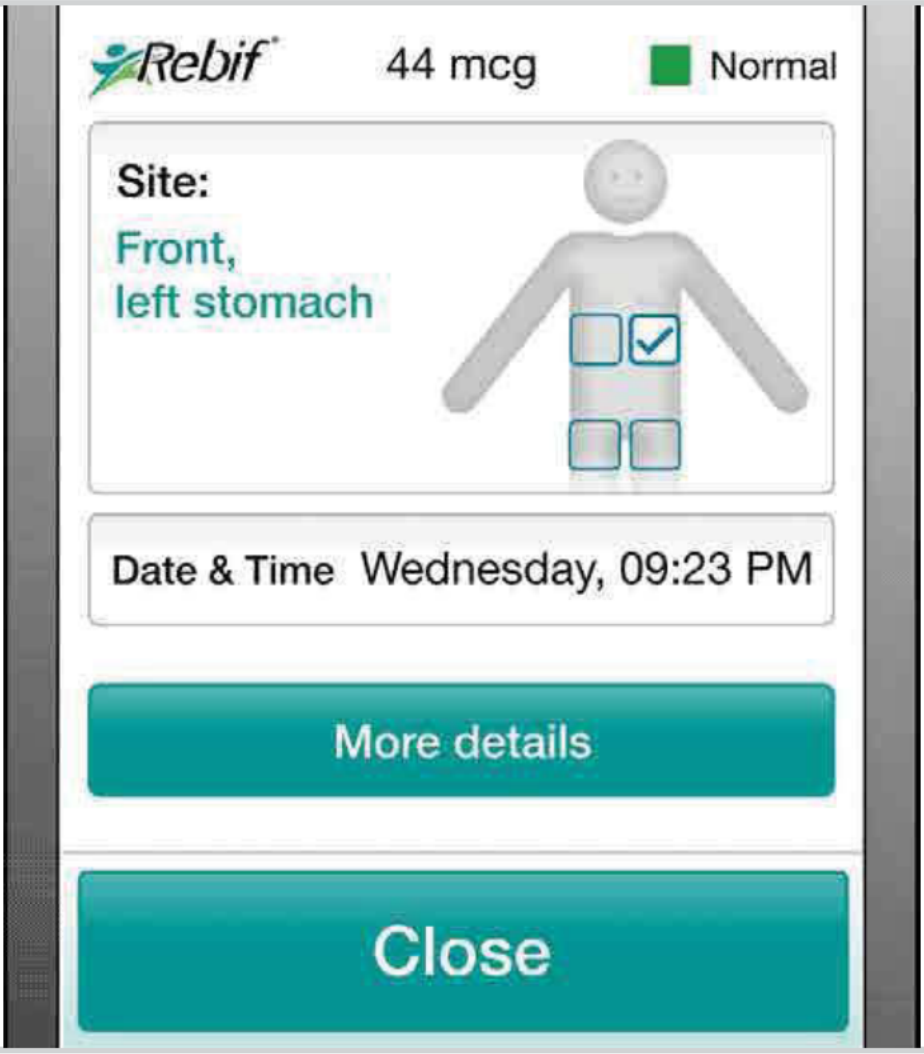


The Calendar Legend screen will appear.

Calendar Tab
View Injection

You can access the View Injection screen by tapping on a day.

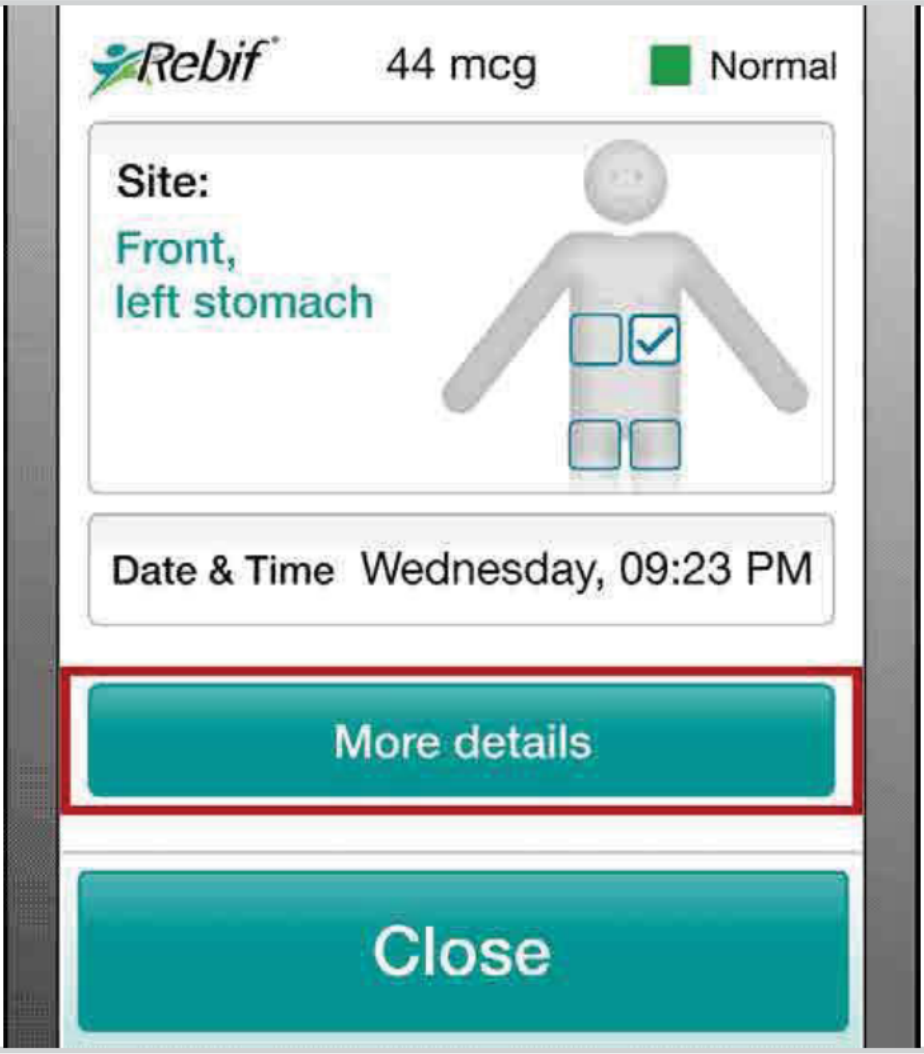
Calendar Tab
View Injection



The View Injection screen will appear, showing the:

- Injection site on your body
- Injection date and time
- More details button

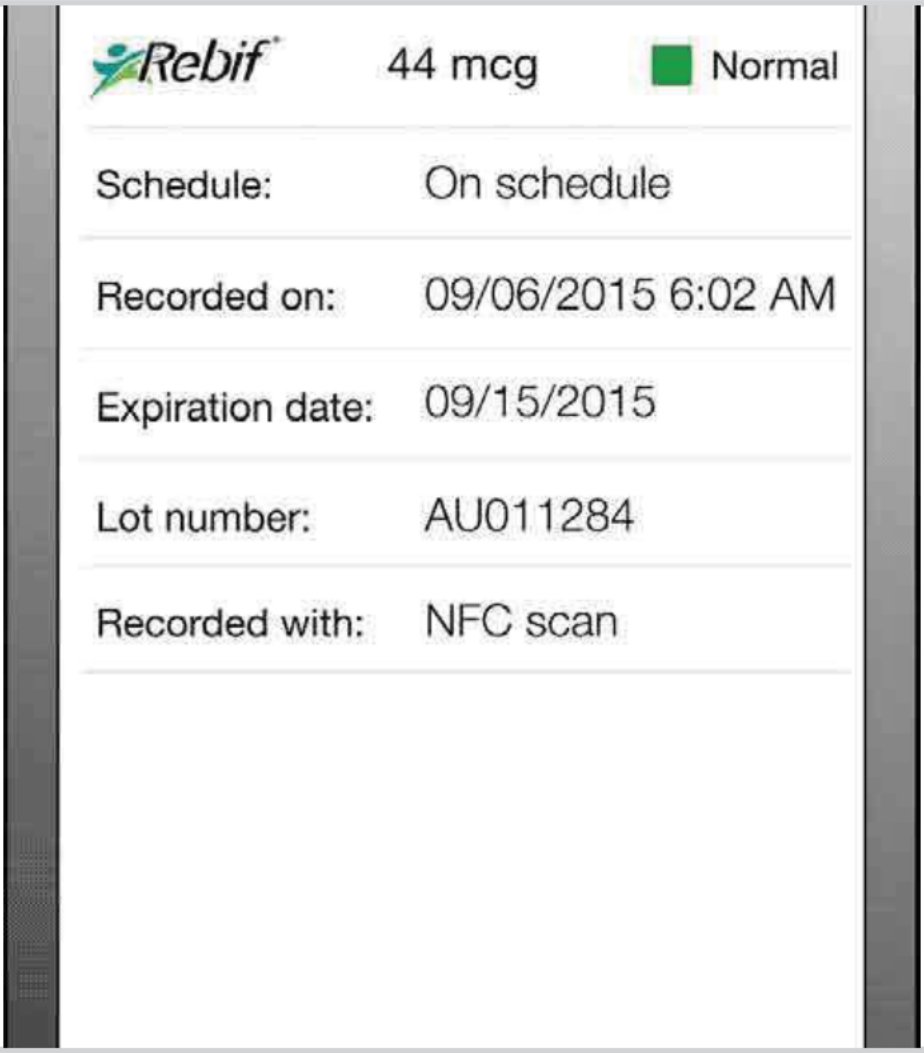
Calendar Tab
More Injection Details



Tap the More details button to access additional injection information on the More injection details screen.

Reference ID: 3991333

Calendar Tab
More Injection Details



On the More Injection Details screen you can review the:

- Rebif dose
- The injection status
- The injection date and time

Calendar Tab
More Injection Details

- The injection expiration date (optionally)
- Medication LOT number (optionally)
- And how the injection was recorded

NOTE:

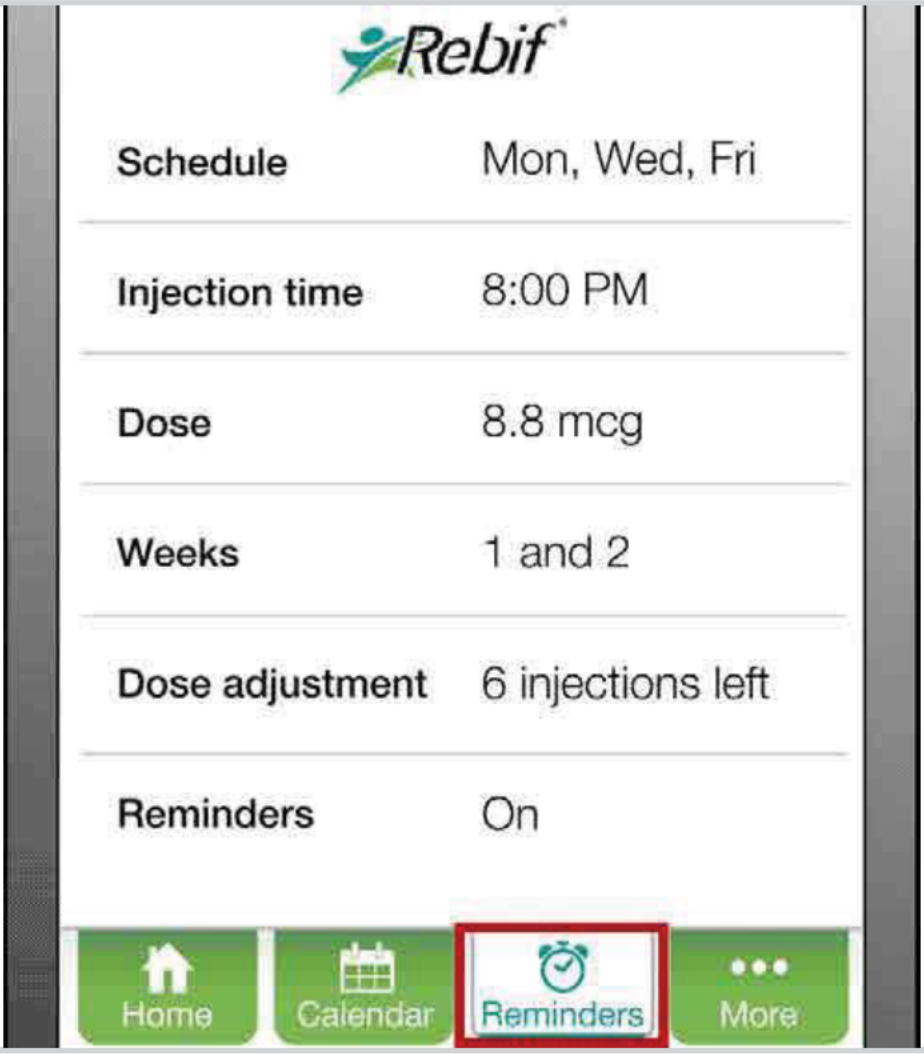
To return to the View Injection screen, tap the Back button.

Reference ID: 3991333

Reminders Tab

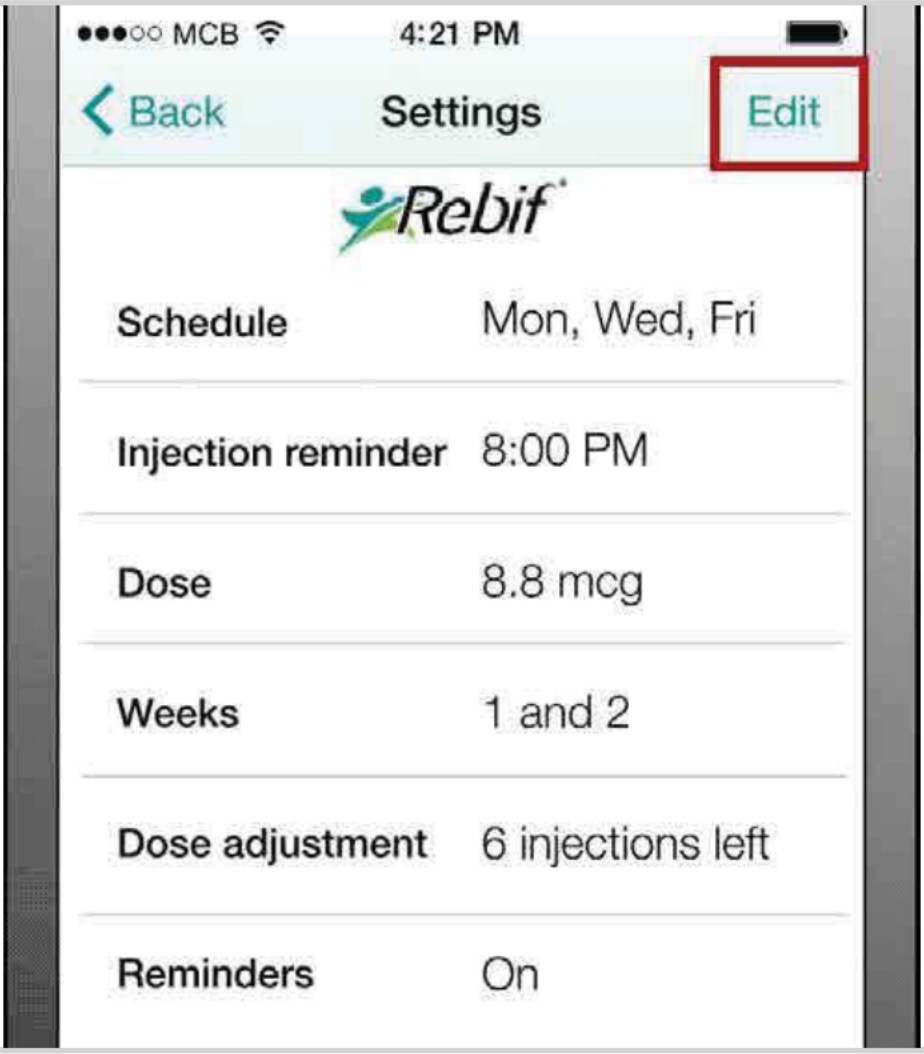
Reference ID: 3991333

Reminders Tab
View Reminder Settings



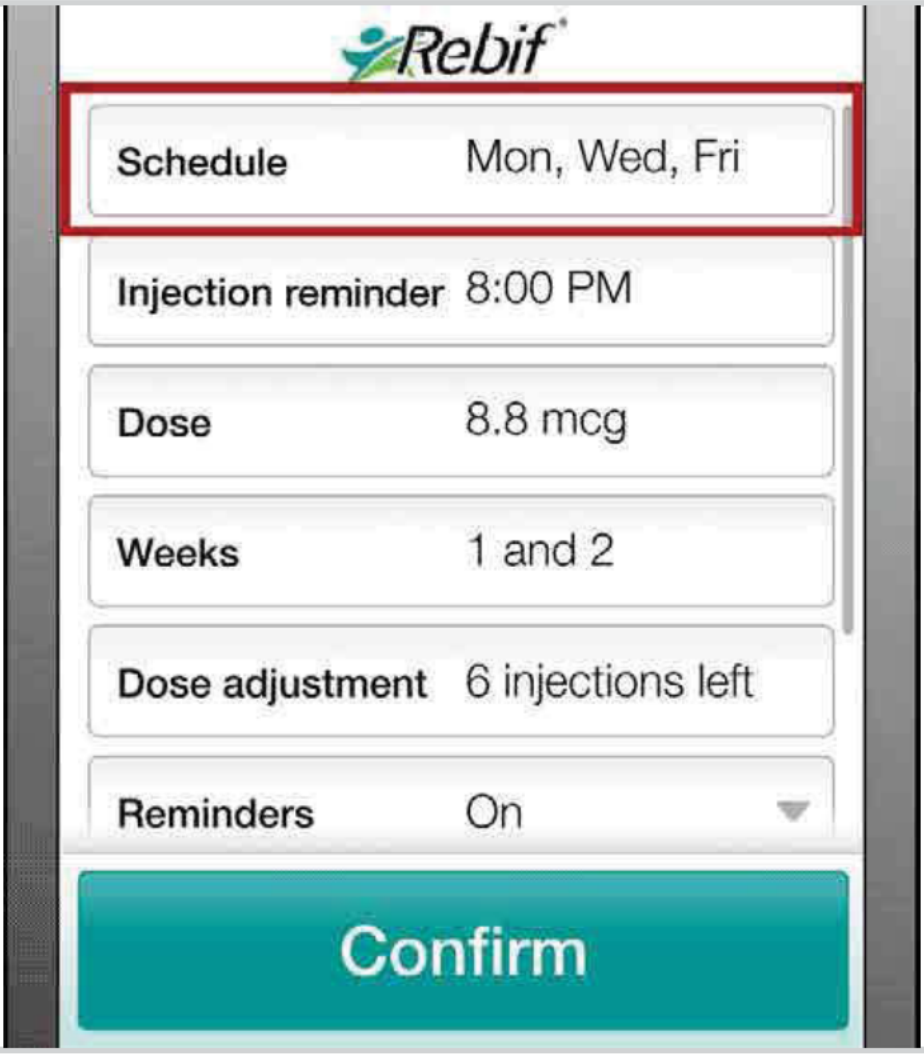
To view MSdialog™ Mobile Application's current reminder settings, tap the Reminders tab. The Reminders page will appear.

Reminders Tab
Edit Reminder Settings



1. Tap the **Edit** button. The Edit settings screen will appear.

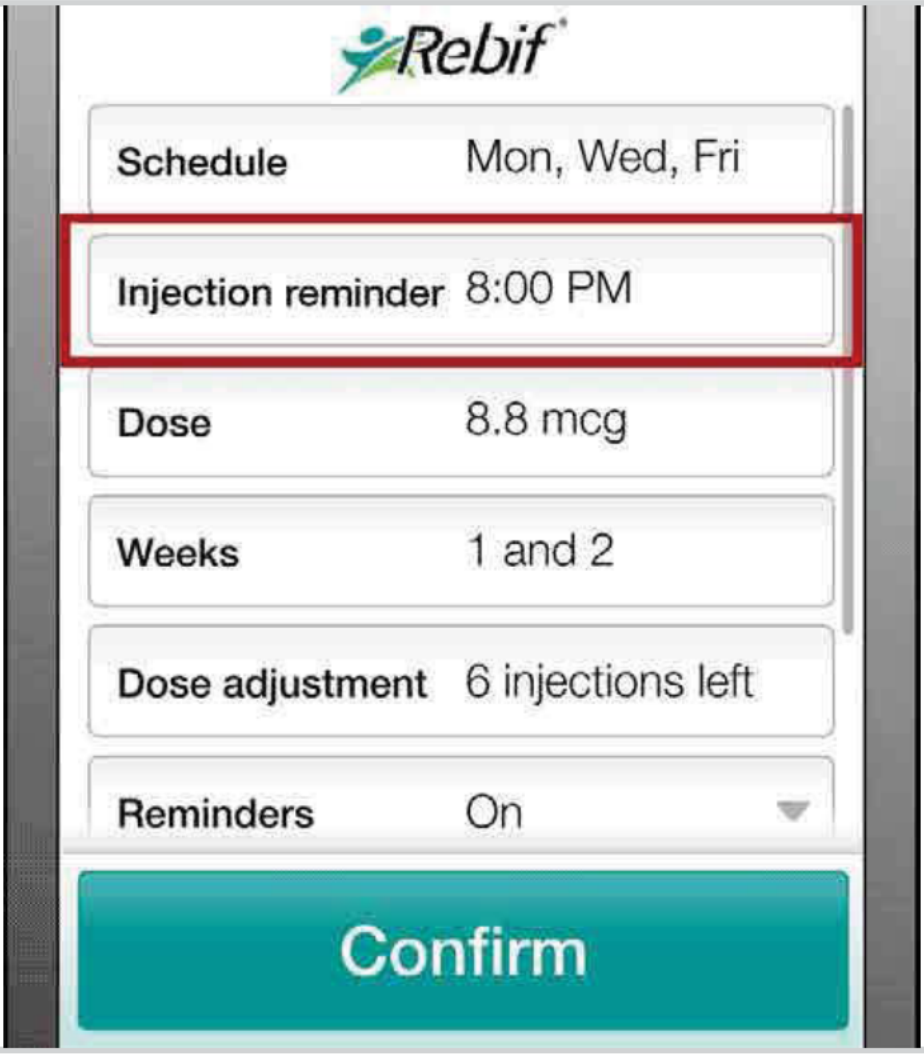
Reminders Tab
Edit Reminder Settings



2. Tap:

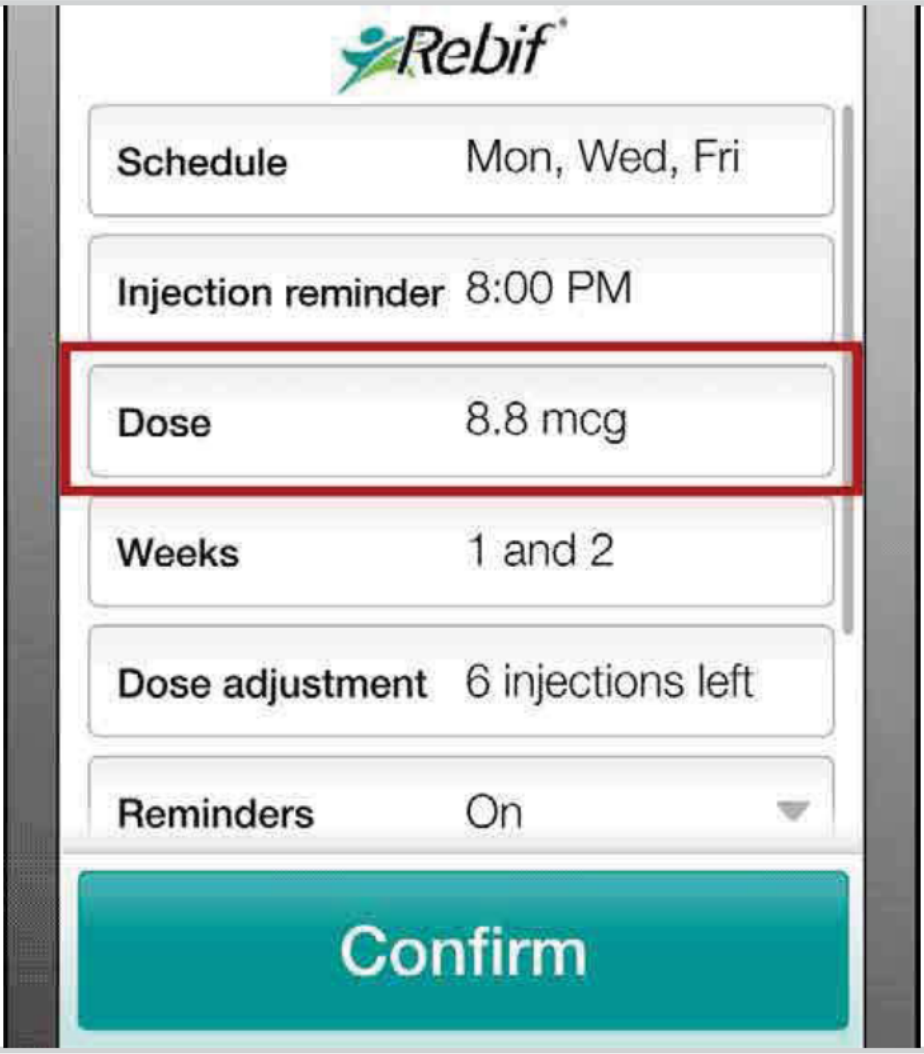
- The Schedule button to change the days per week in which you want to be reminded to inject.

Reminders Tab
Edit Reminder Settings



- The Injection reminder button to change the timing of your injection during the day.

Reminders Tab
Edit Reminder Settings



- The Dose button to change the dose for your treatment.

Reference ID: 3991333

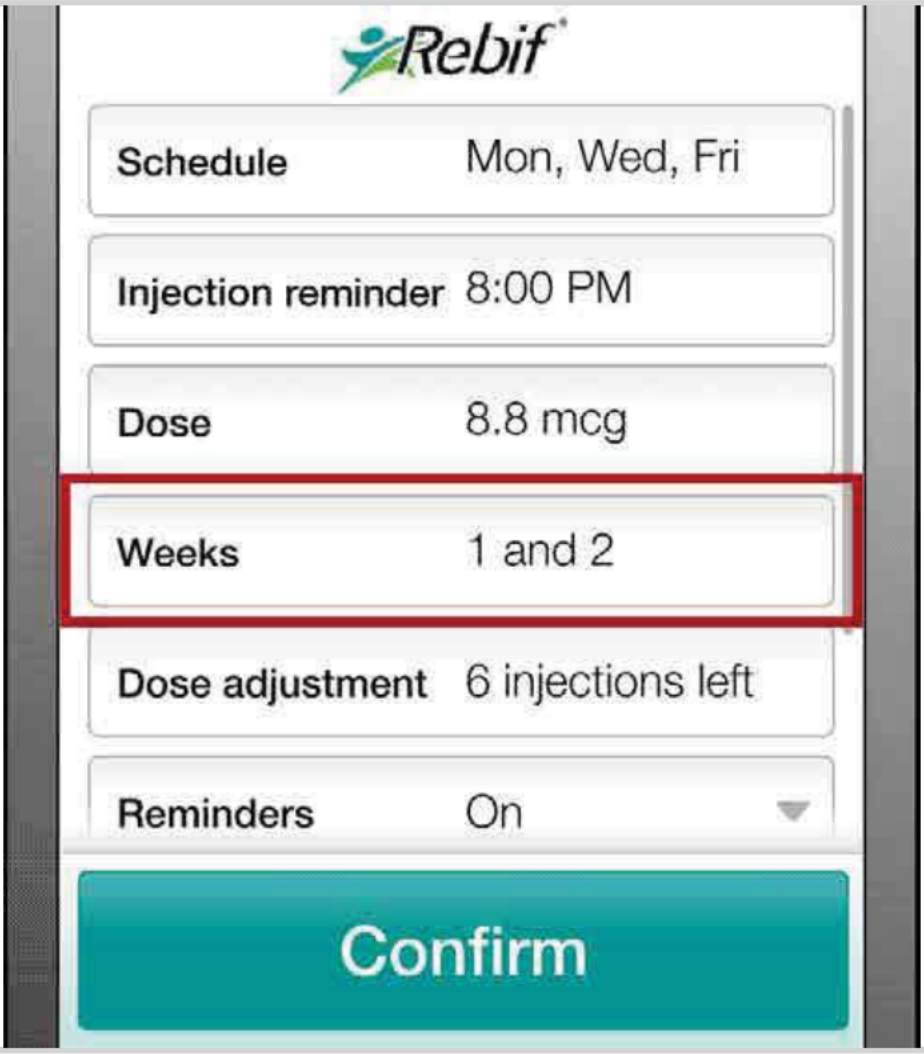
Reminders Tab
Edit Reminder Settings

⚠ CAUTION:

MSdialog™ Mobile Application's dose settings are not intended to replace the prescription from your doctor. Please use the Application only to record your prescribed dose settings.

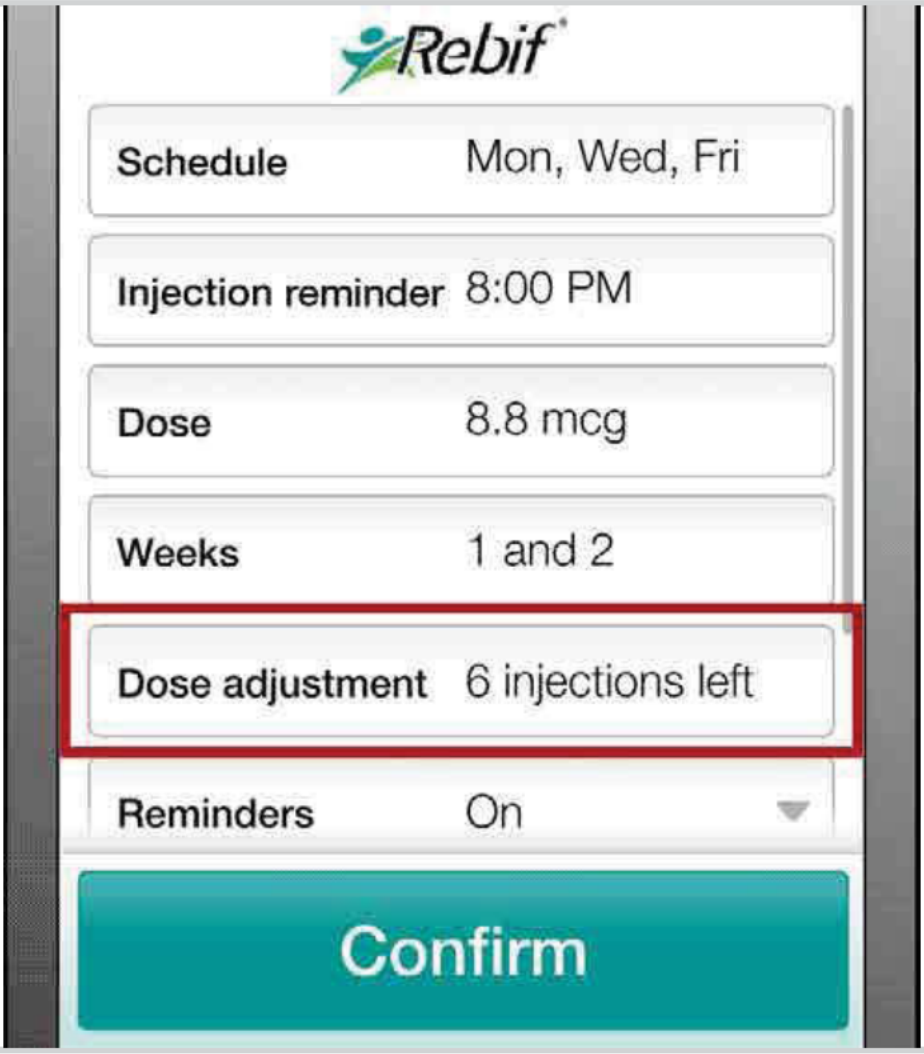
Reference ID: 3991333

Reminders Tab
Edit Reminder Settings



- If you are on Titration, tap the Weeks button to change the number of the week in which your treatment is running.

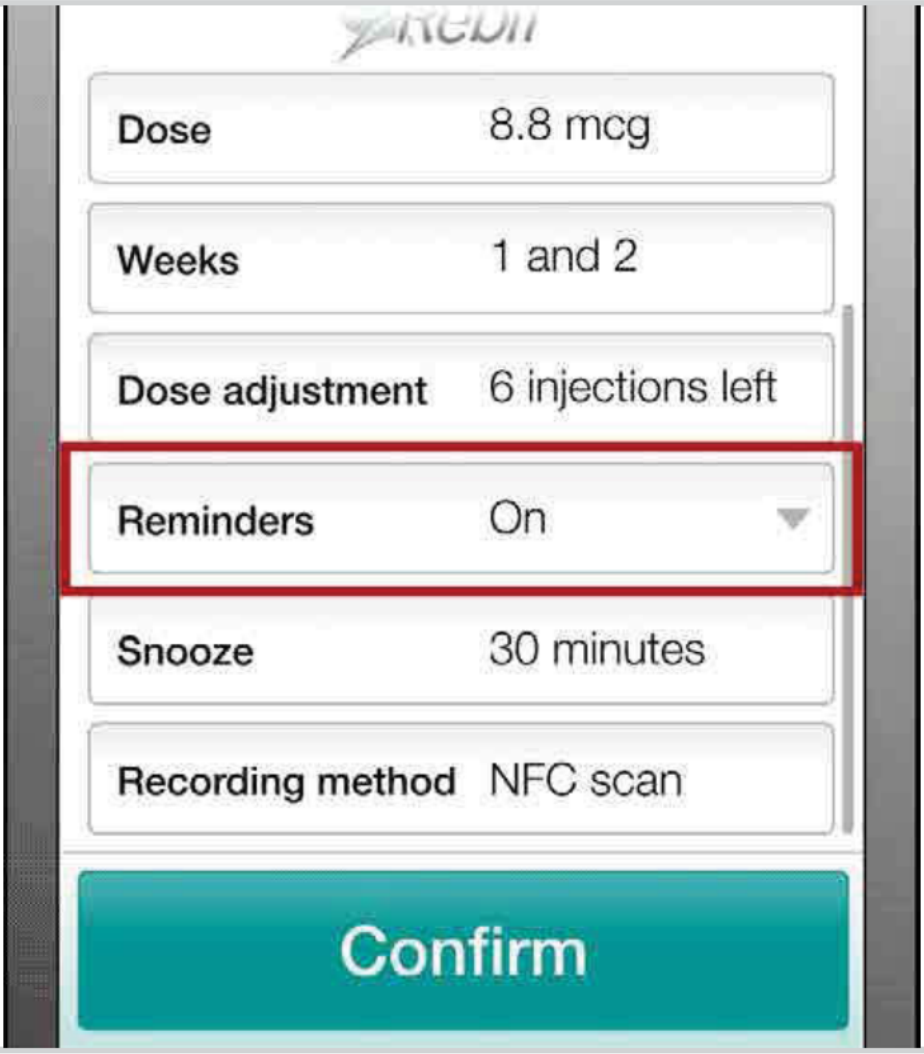
Reminders Tab
Edit Reminder Settings



- If you are on Titration, tap the Dose adjustment button to change the number of injections left to complete your titration phase.

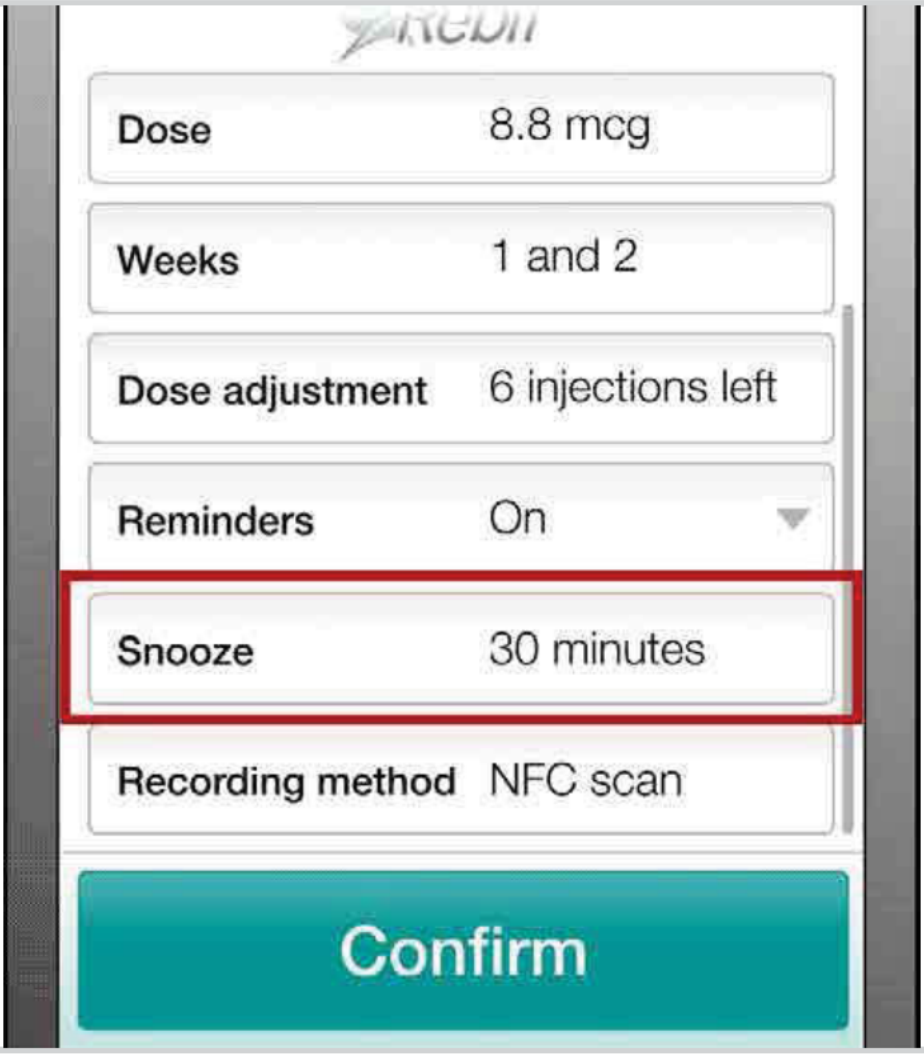
Reference ID: 3991333

Reminders Tab
Edit Reminder Settings



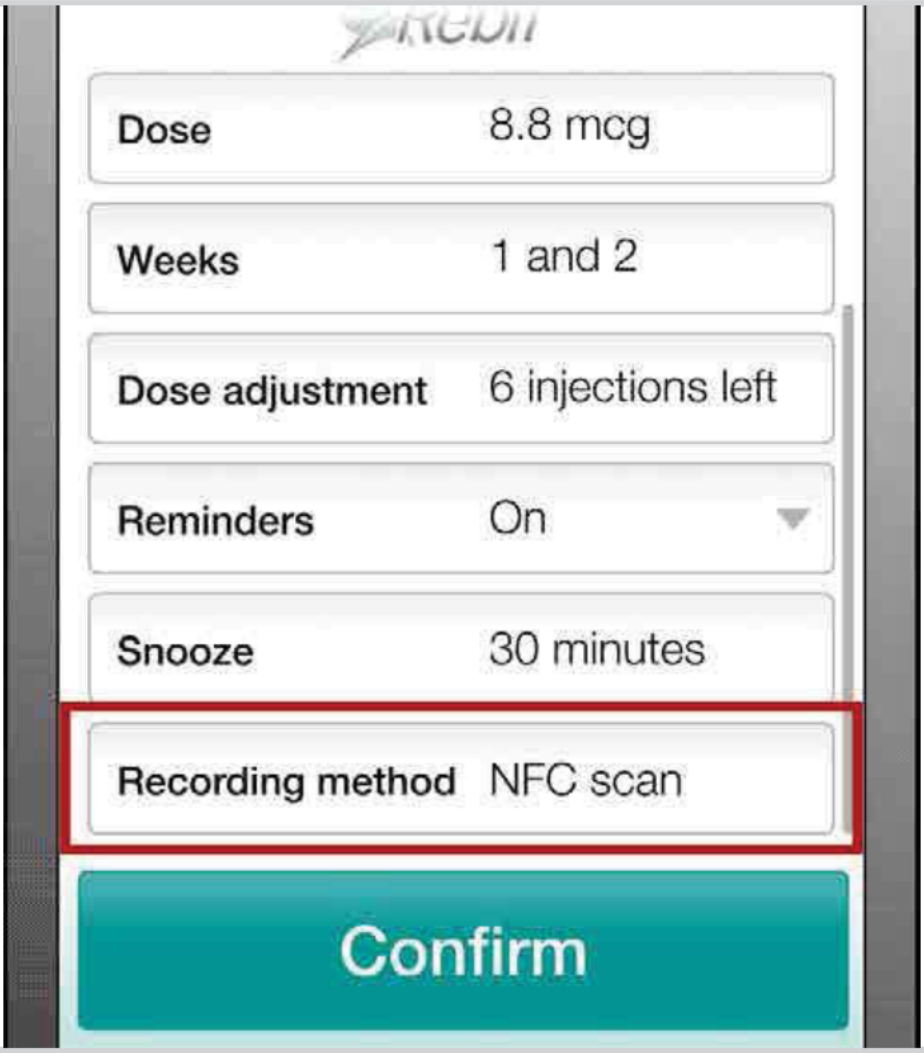
- The Reminders button is for turning On or Off the injection's notifications.

Reminders Tab
Edit Reminder Settings

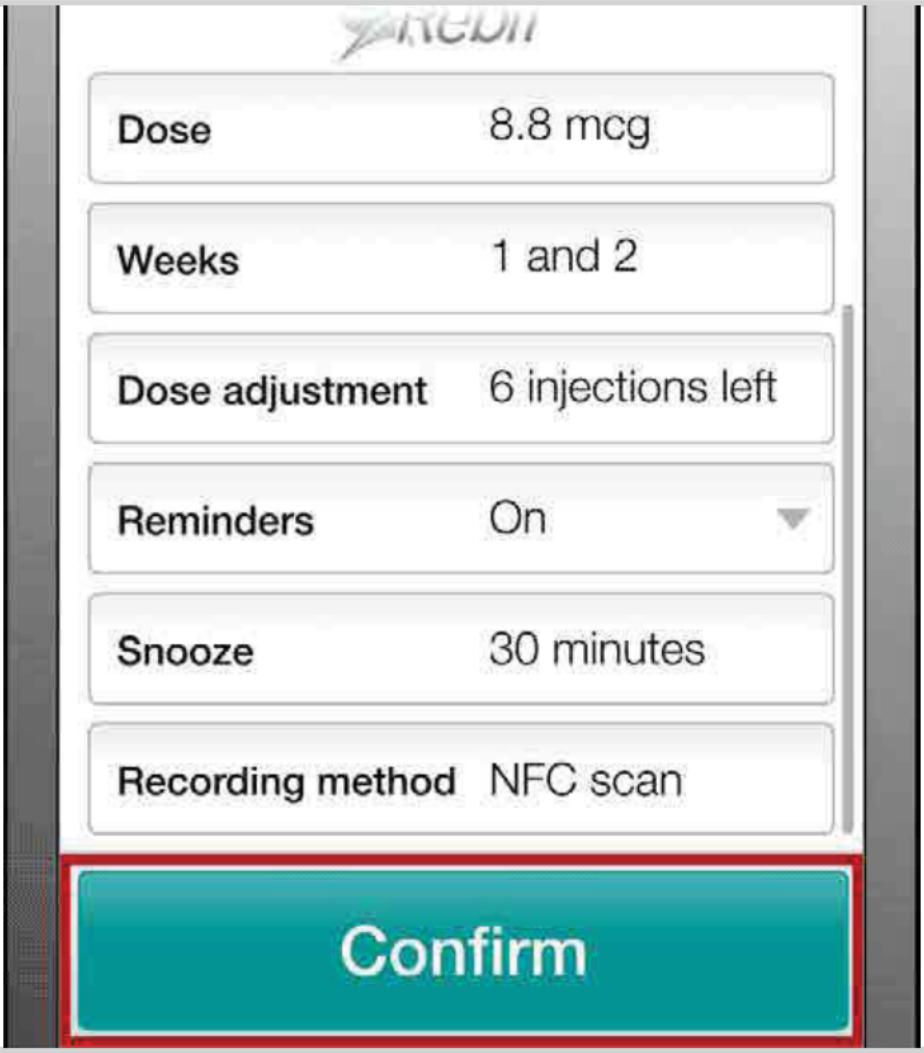


- The Snooze button is for selecting the interval of time when the reminder alarm will repeat.

Reminders Tab
Edit Reminder Settings

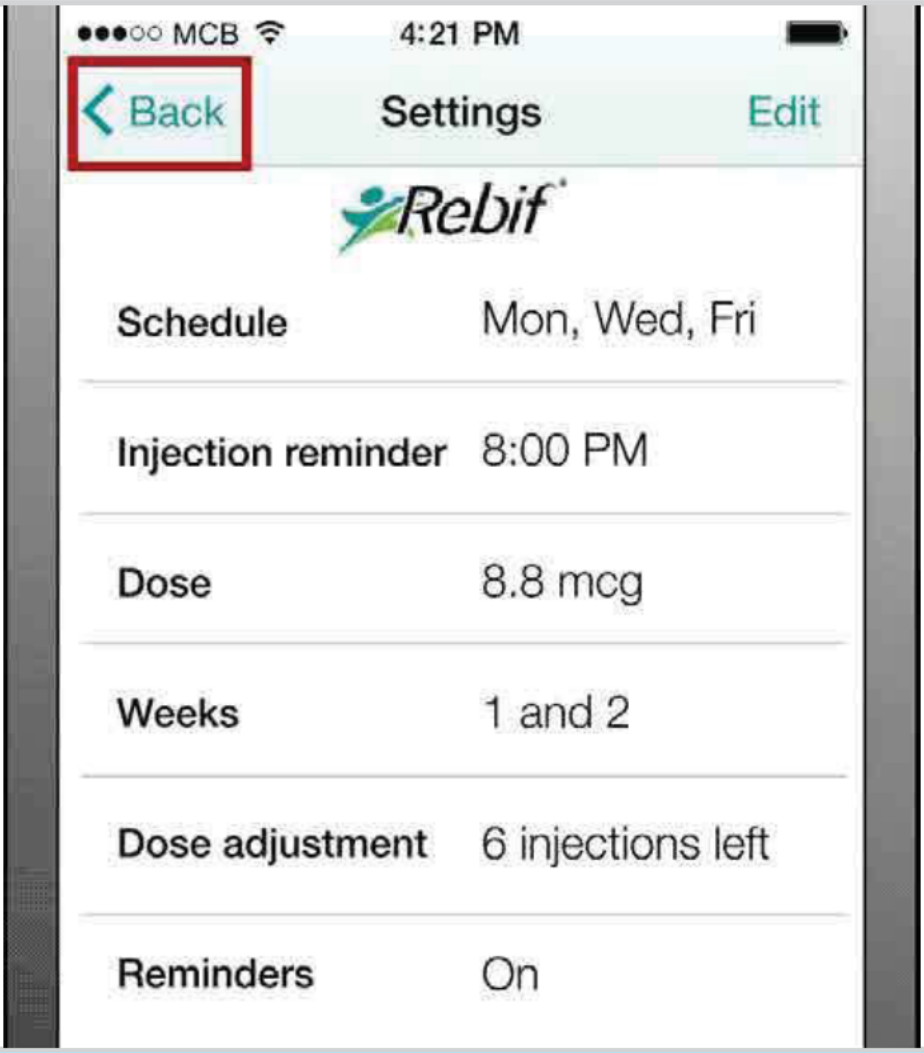


- Tap the Recording method button to select the method to use to record an injection in the application.



3. Tap the Confirm button to apply your changes.

Reminders Tab
Edit Reminder Settings



NOTE:

To return to the Reminders Settings screen without changing any injection details, tap the Back button.

Reminders Tab
Edit Reminder Settings

⚠ CAUTION:

Always check the Reminders tab if you start using MSdialog™ Mobile Application again after you stopped using it for a while. The scheduled injections' details might not be aligned with your actual injection schedule.

Reference ID: 3991333

Responding to Reminders If you set up reminders for injections, a reminder will appear at the time you specified. When the reminder is displayed, you can view details about the scheduled injection, record the injection, or snooze the reminder.

Reference ID: 3991333

More Tab

Reference ID: 3991333

About the More Tab

This section provides information about:

- Managing your account
- Accessing help & support
- Terms and Conditions
- MSdialog™ Mobile Application

Reference ID: 3991333

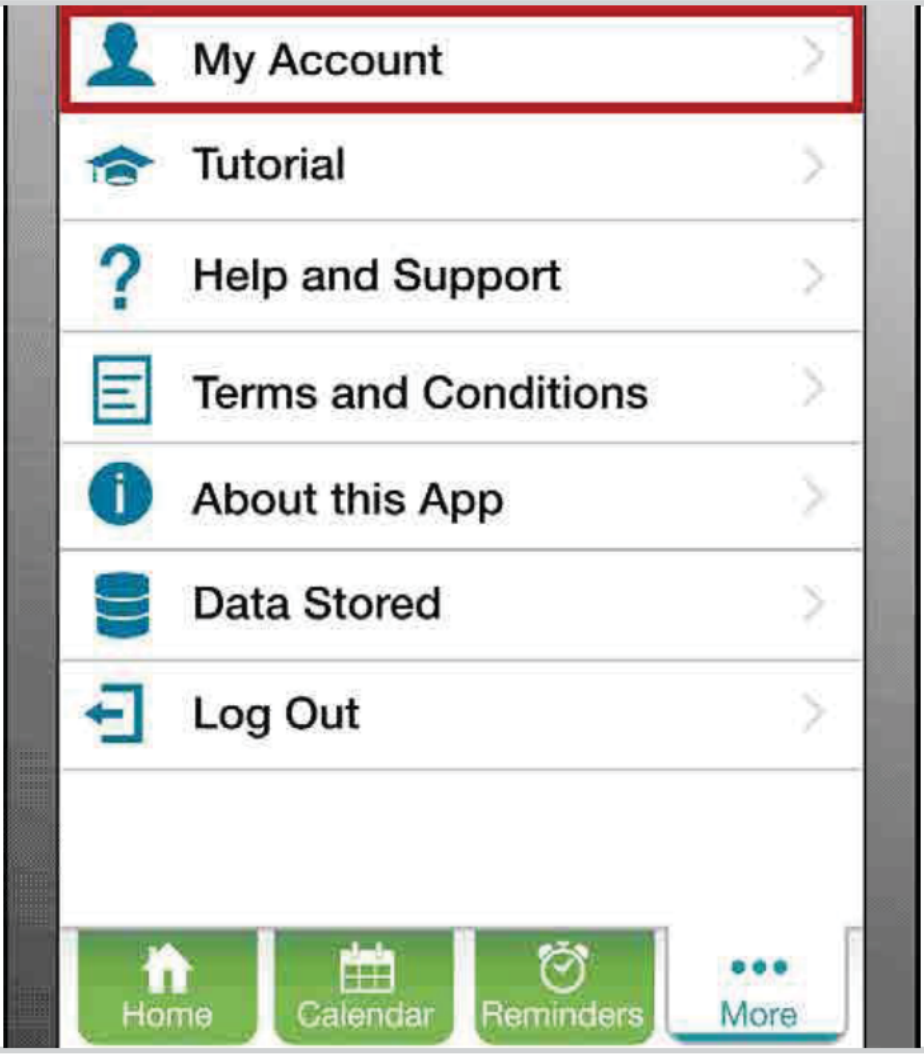
More Tab
My Account

This section explains:

- How to view your profile
- Change your password
- Request closure of your account

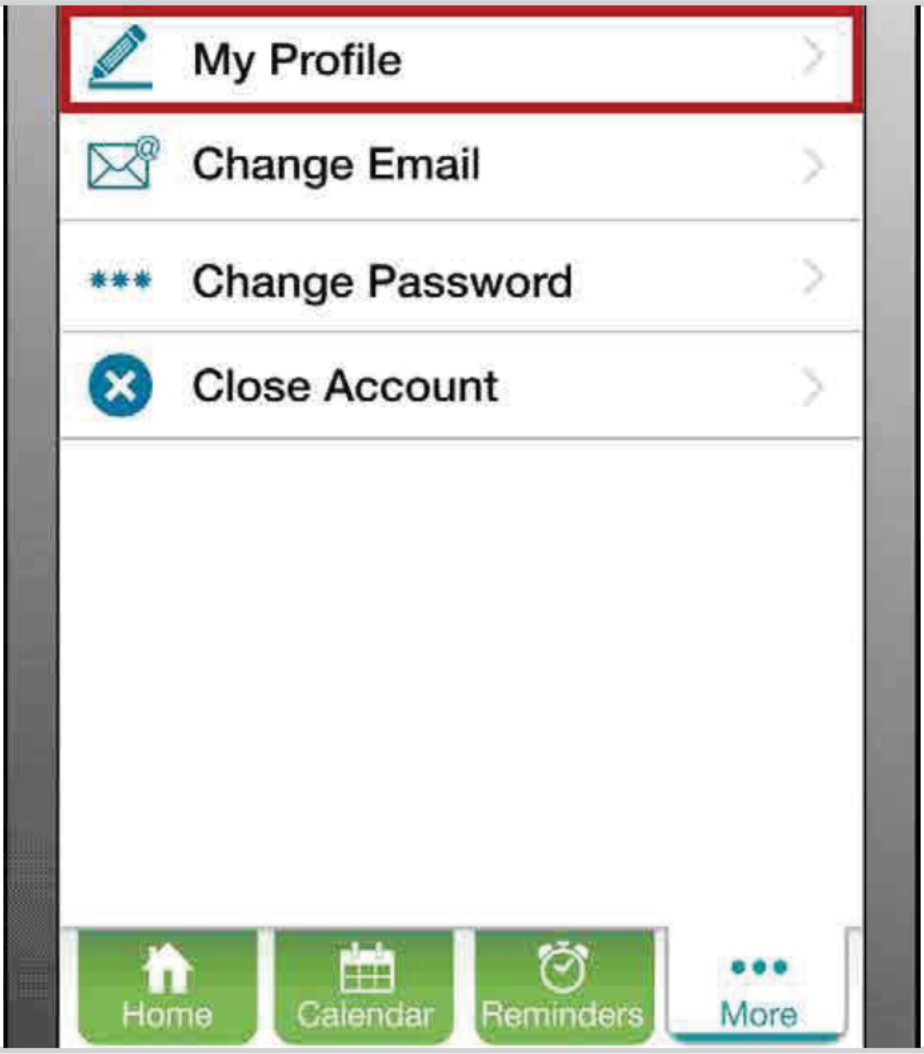
Reference ID: 3991333

More Tab
My Account



1. Tap My account on the More screen. The My account menu will appear.

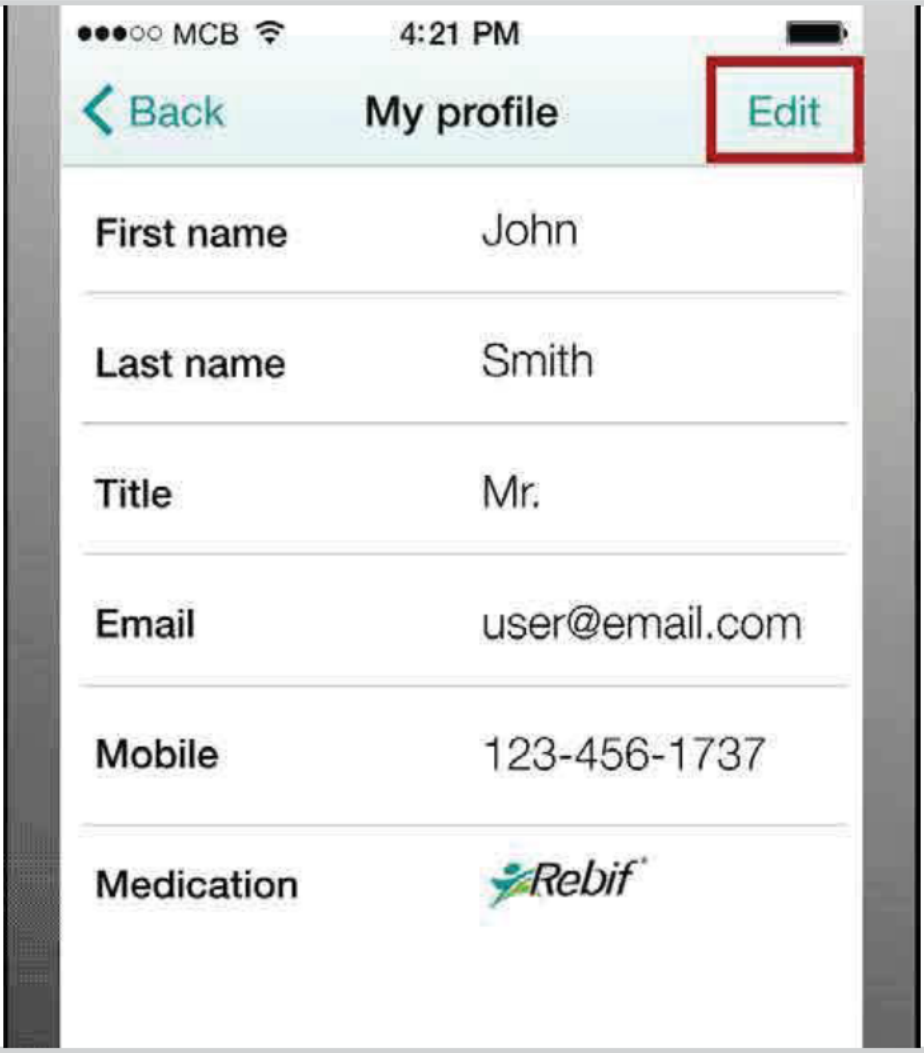
More Tab
My Account



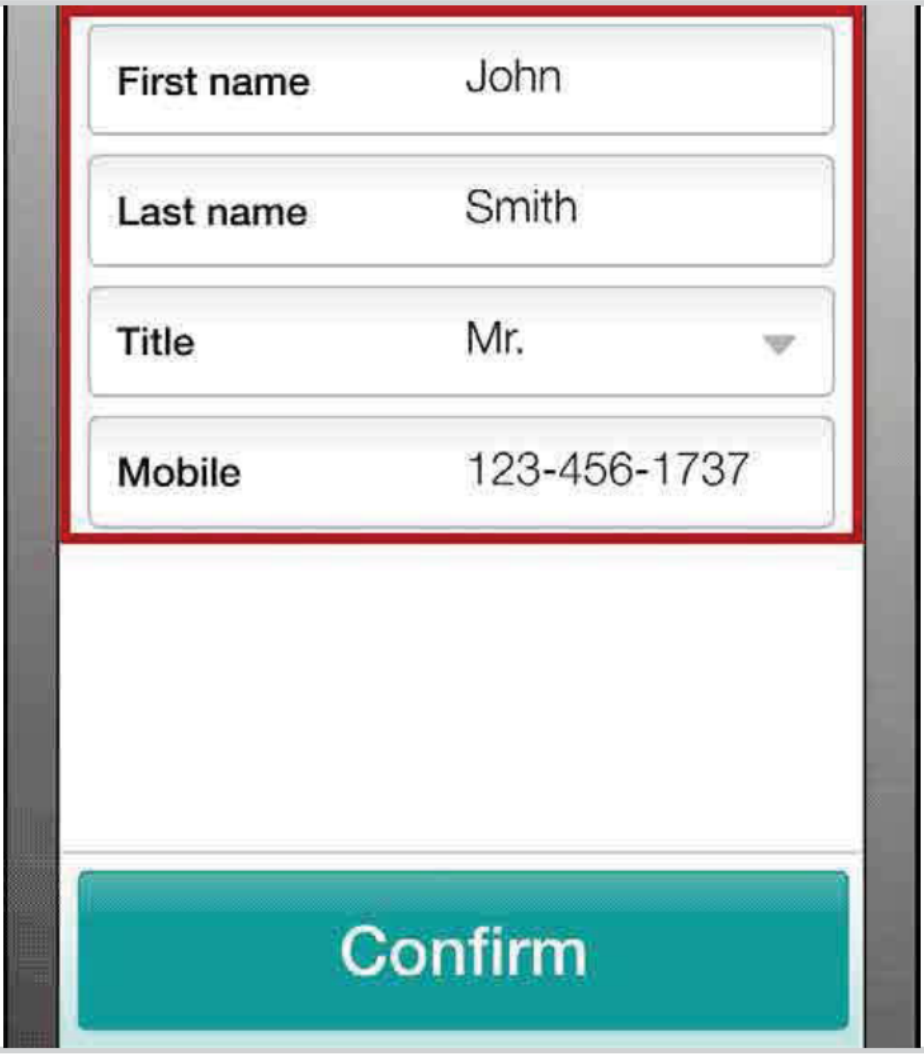
2. Tap My profile button. The My profile page will appear.

Reference ID: 3991333

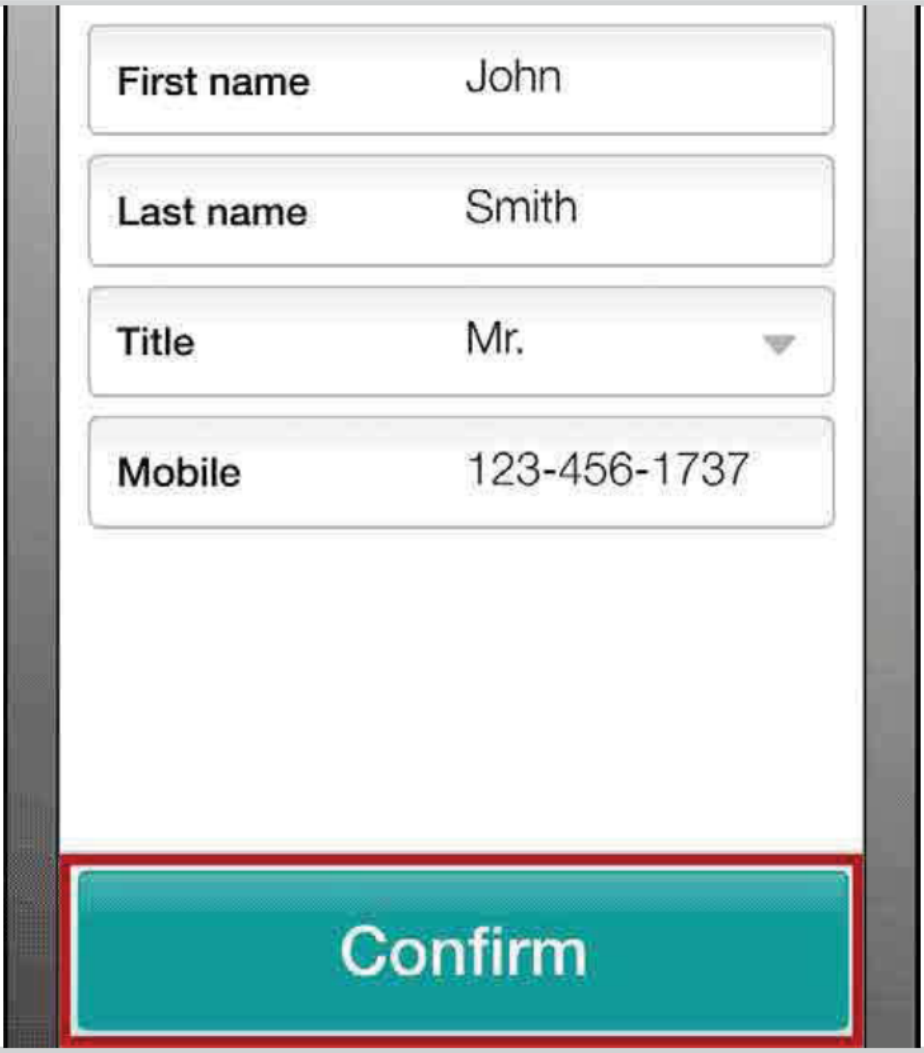
More Tab
My Account



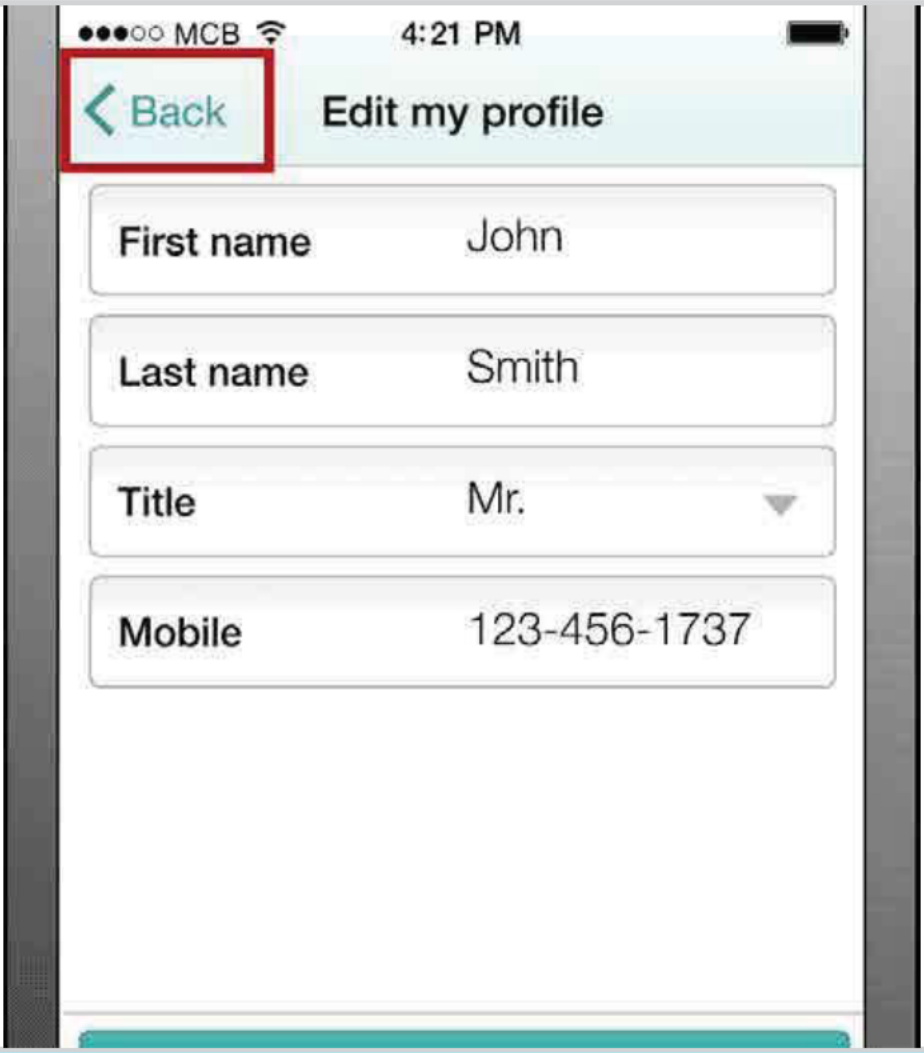
3. Tap the Edit button. The Edit my profile screen will appear.



4. Change your personal details.



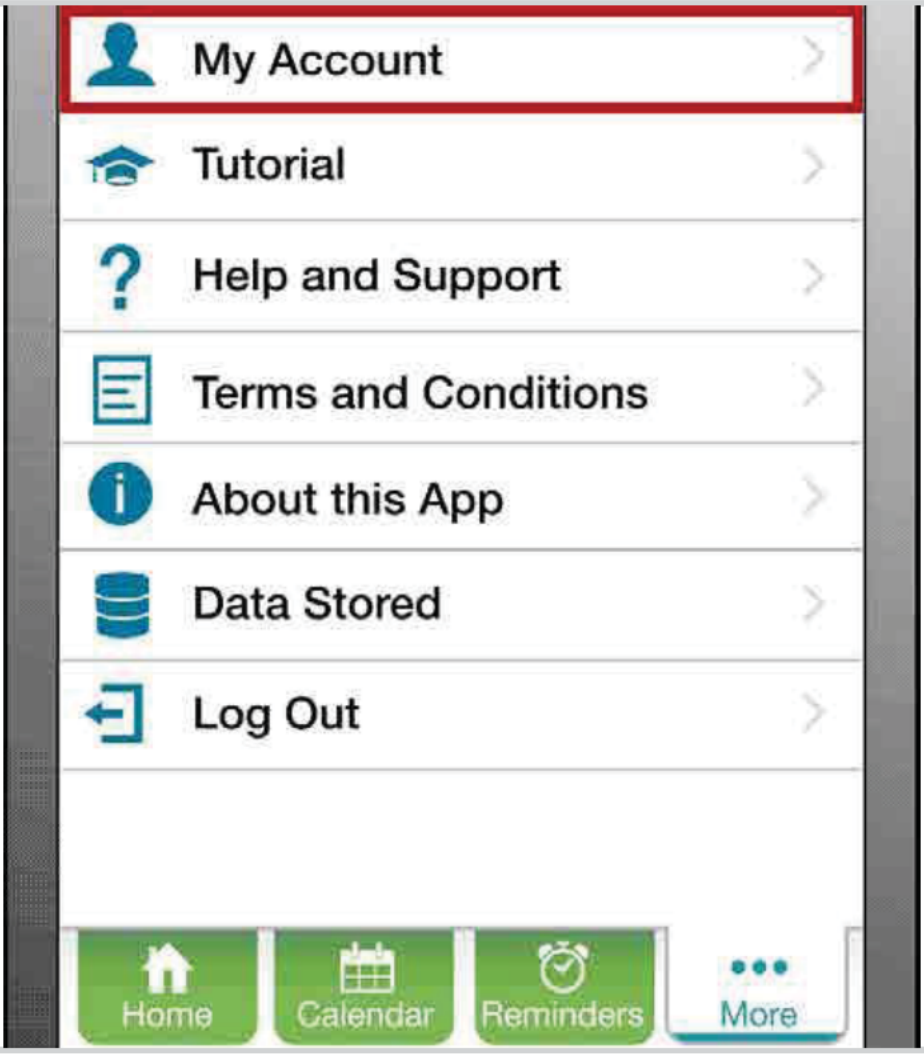
5. Tap the Confirm button to apply your changes.



NOTE:

To return to My profile screen without changing any personal details, tap the Back button.

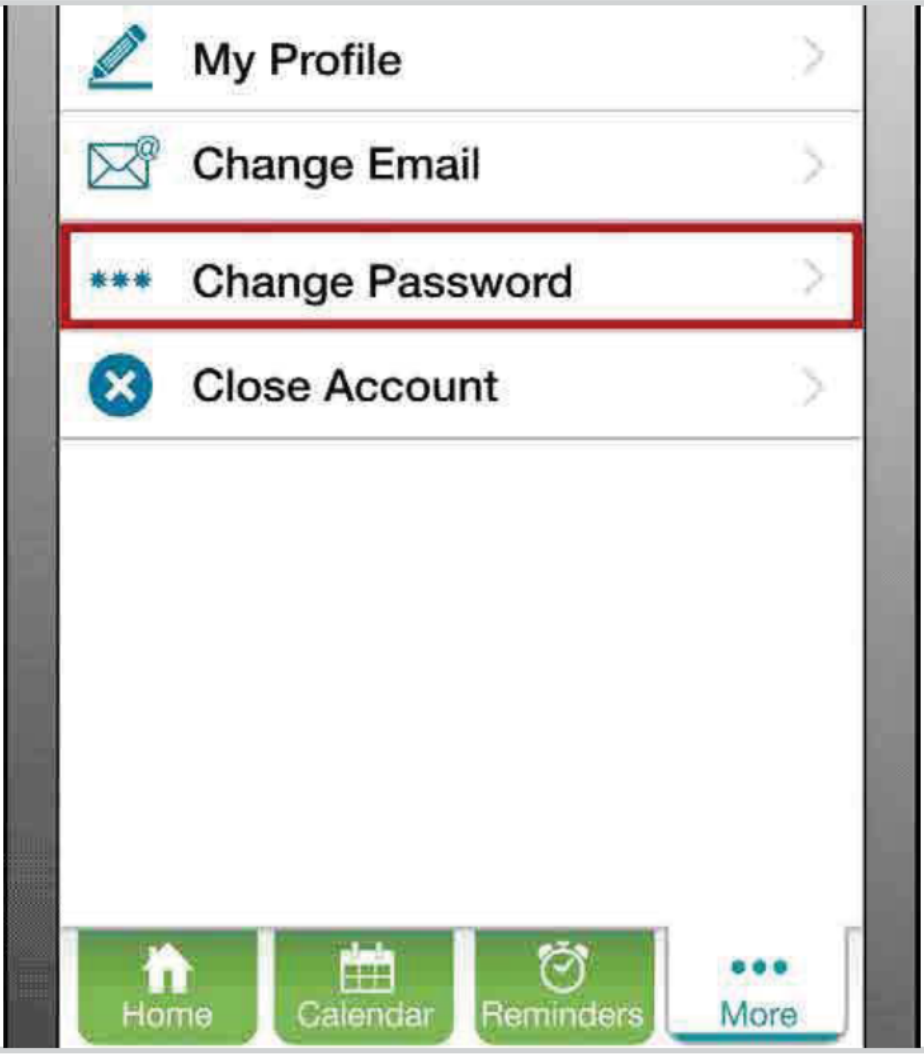
More Tab
Change your Password



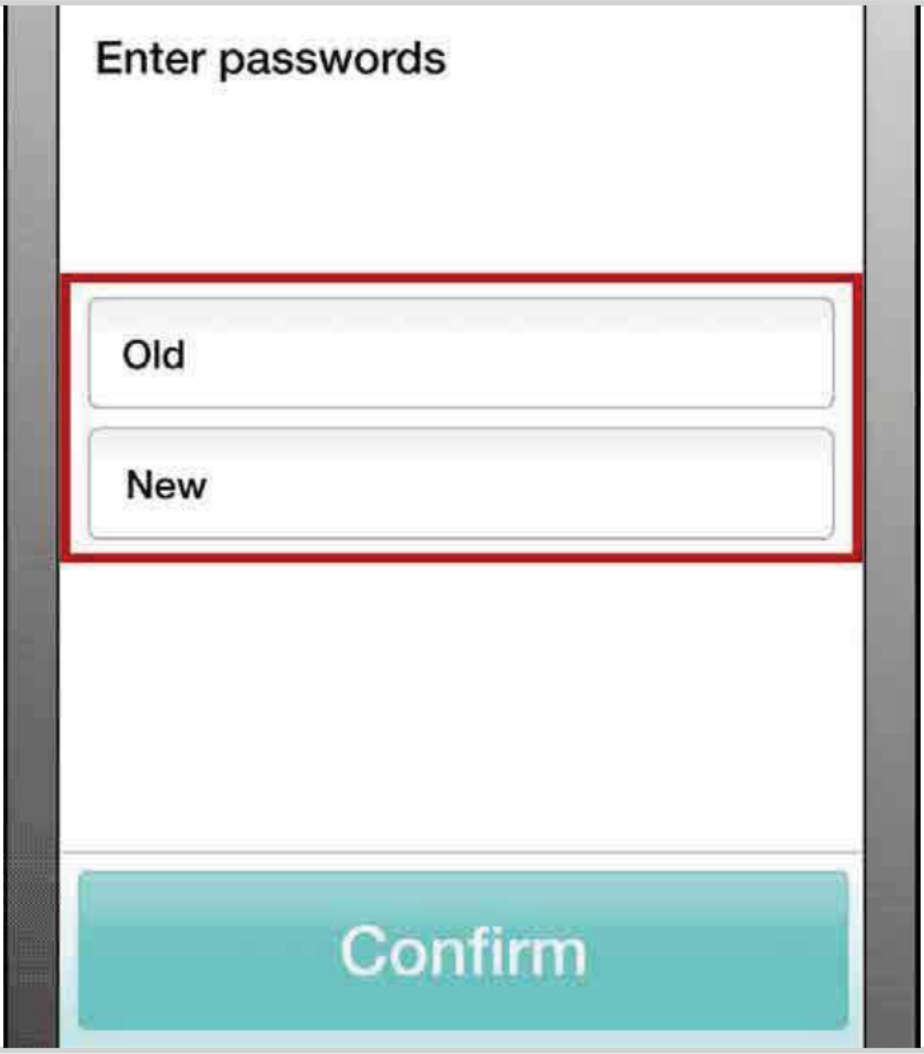
1. Tap My Account on the More screen. The My Account menu will appear.

Reference ID: 3991333

More Tab
Change your Password

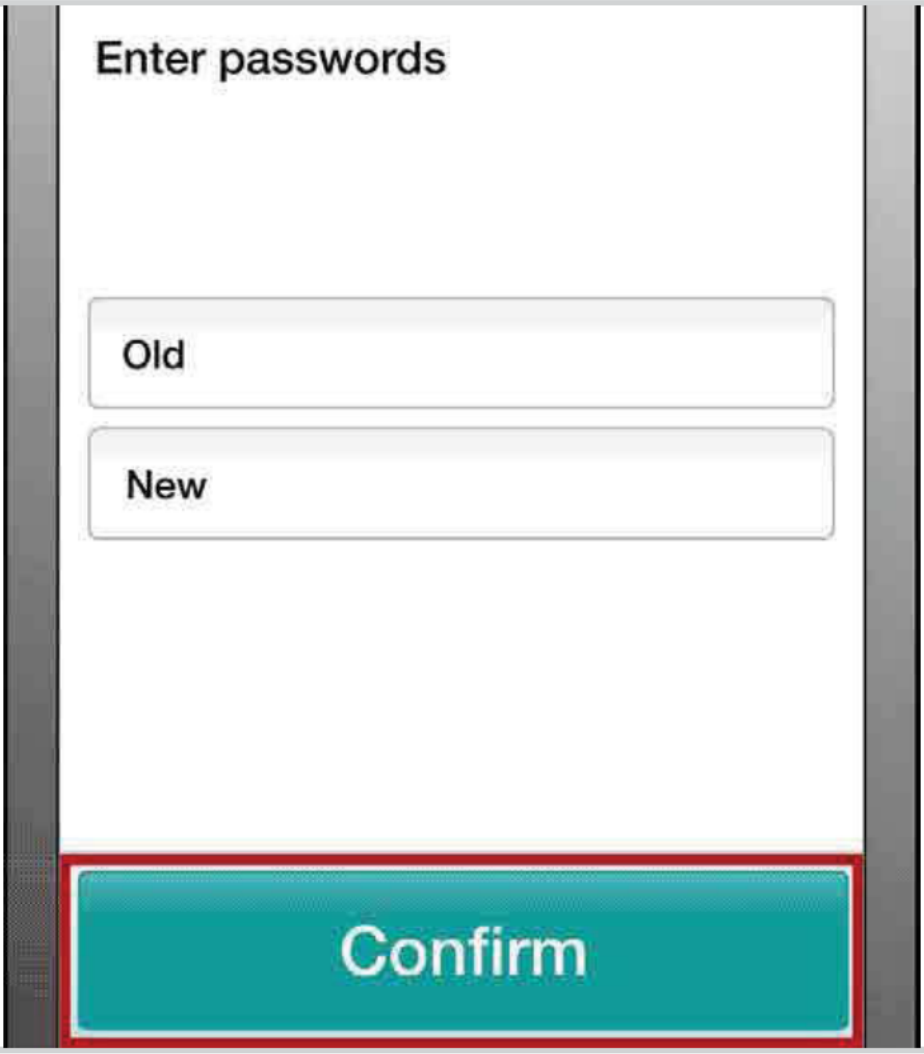


2. Tap Change Password. The Change Password screen will appear.



3. Enter the following information:

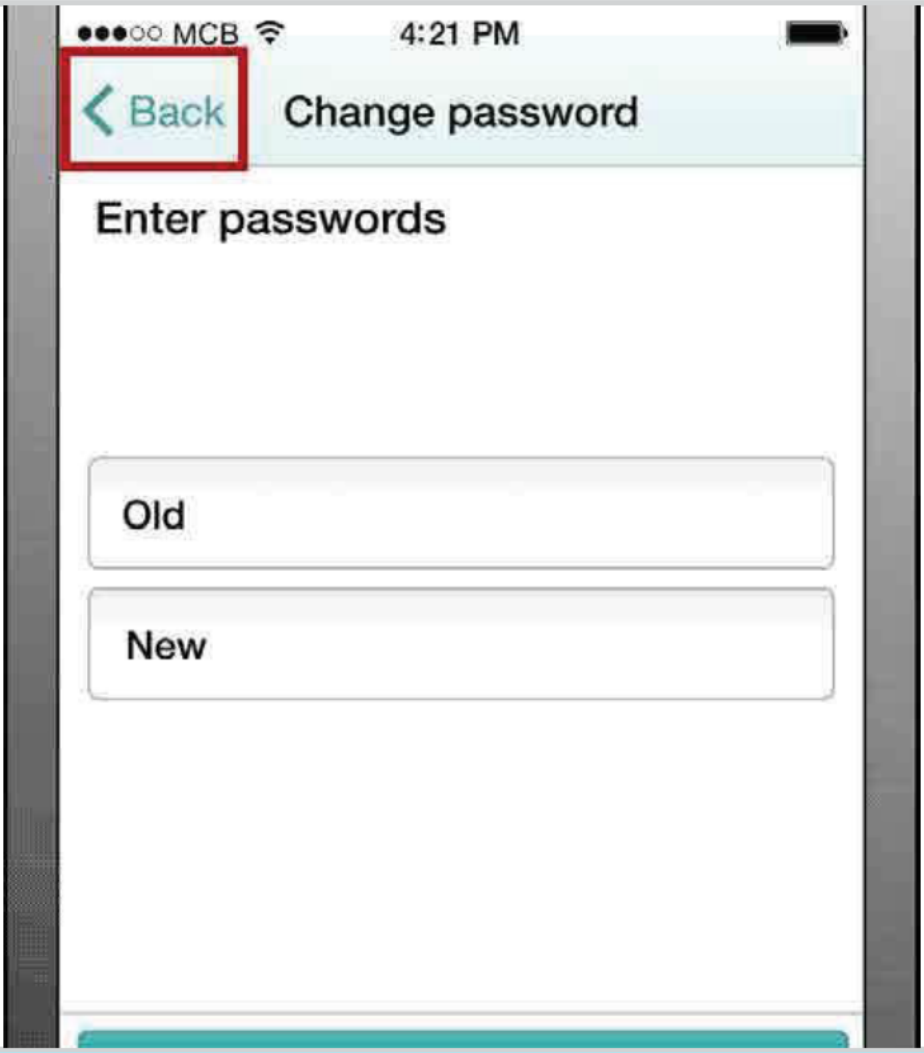
- Old – Type your old password.
- New – Type your new password.



4. Tap the Confirm button.

5. The Notification window will appear indicating that your password has changed. Tap the OK button. The My Account screen will appear.

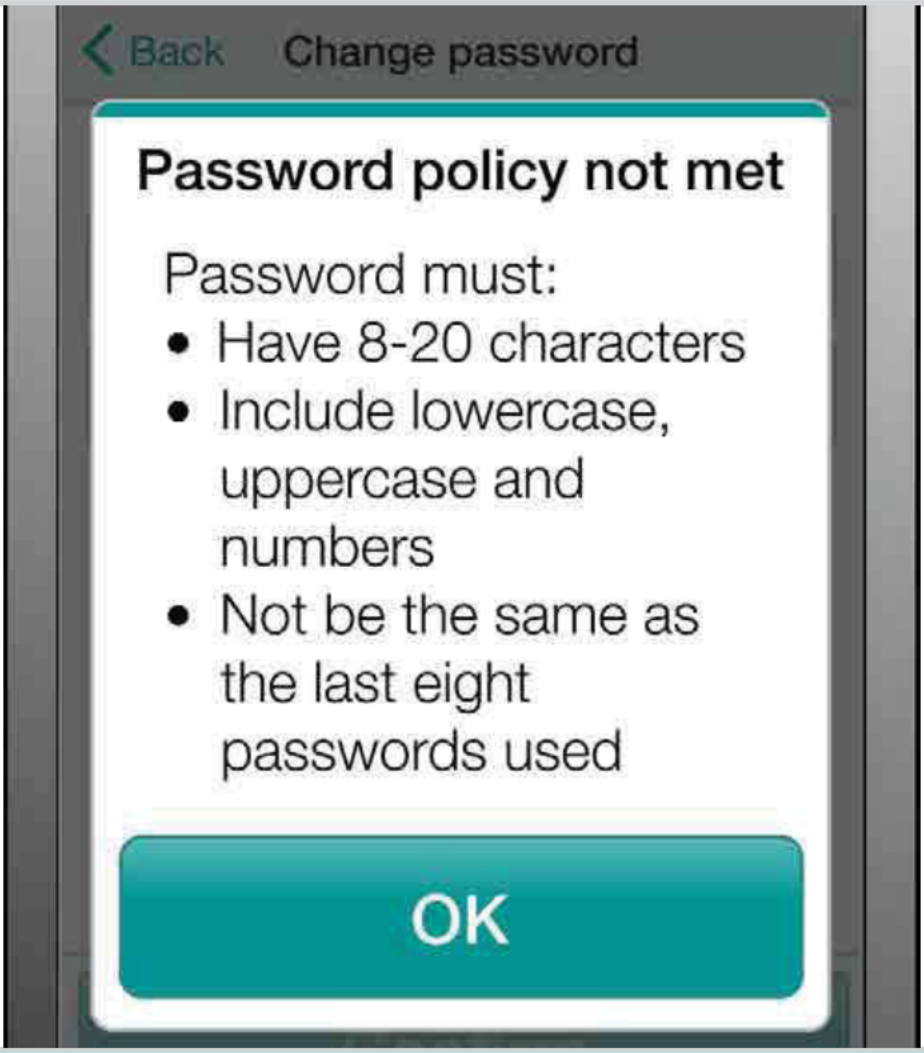
More Tab
Change your Password



NOTE:

To return to My Account screen without changing your password, tap the Back button.

More Tab
Change your Password



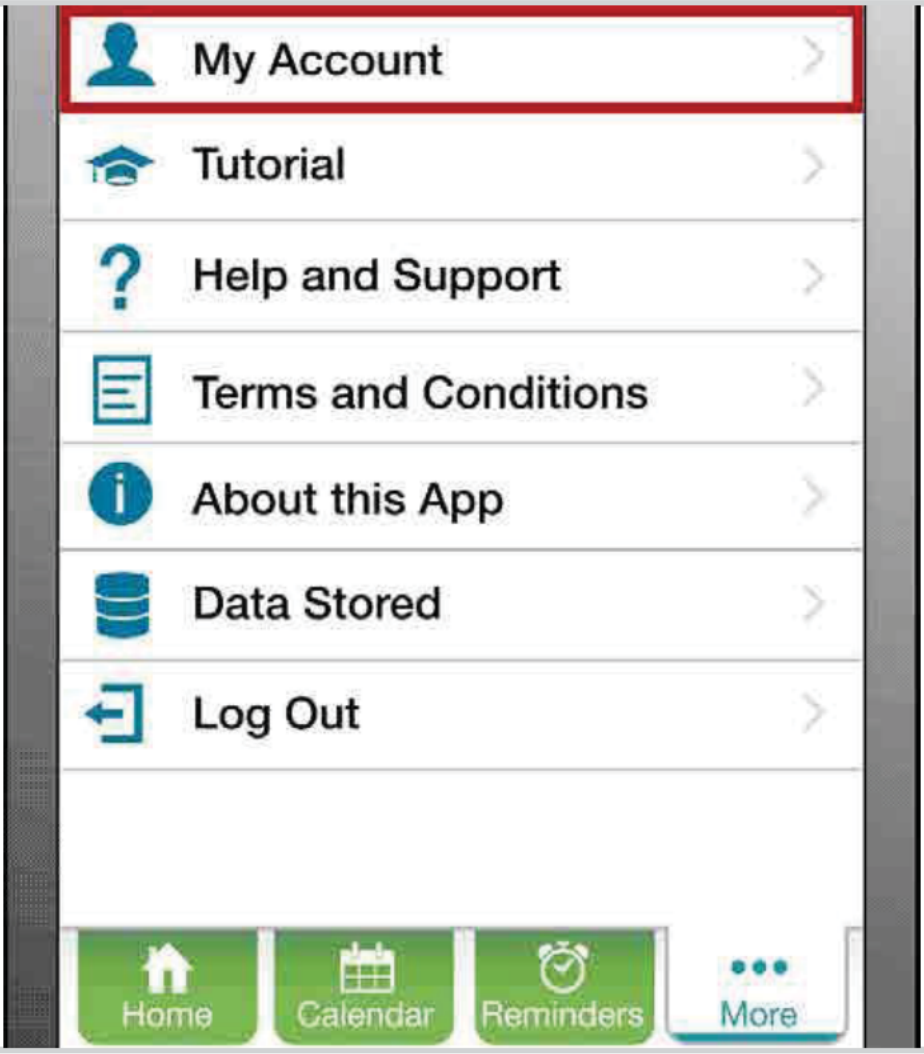
NOTE:

If your new password does not meet the password policy, the application will remind you about the minimum password requirements.

If you no longer wish to use MSdialog™ Mobile Application, you can request closure of your account. When you close your account, you will not be able to access your data or reminders.

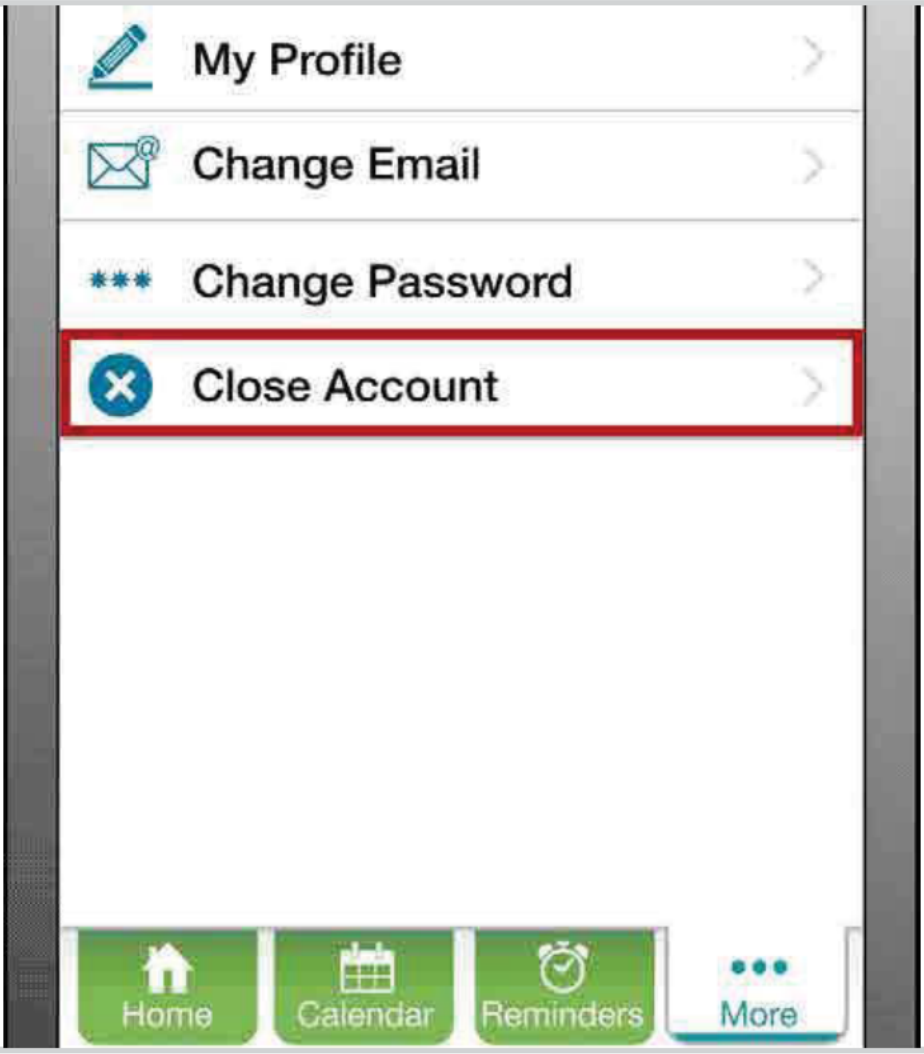
Reference ID: 3991333

More Tab
Close your Account



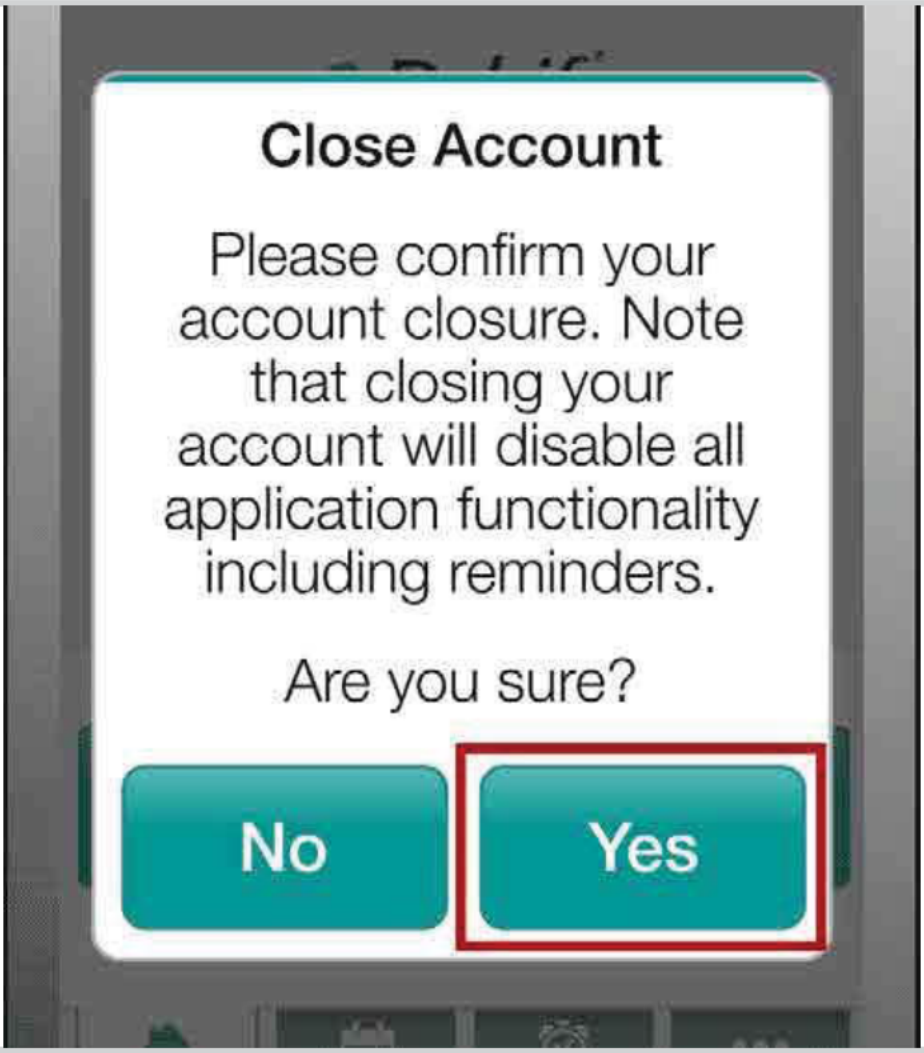
1. Tap My Account on the More screen. The My Account menu will appear.

More Tab
Close your Account

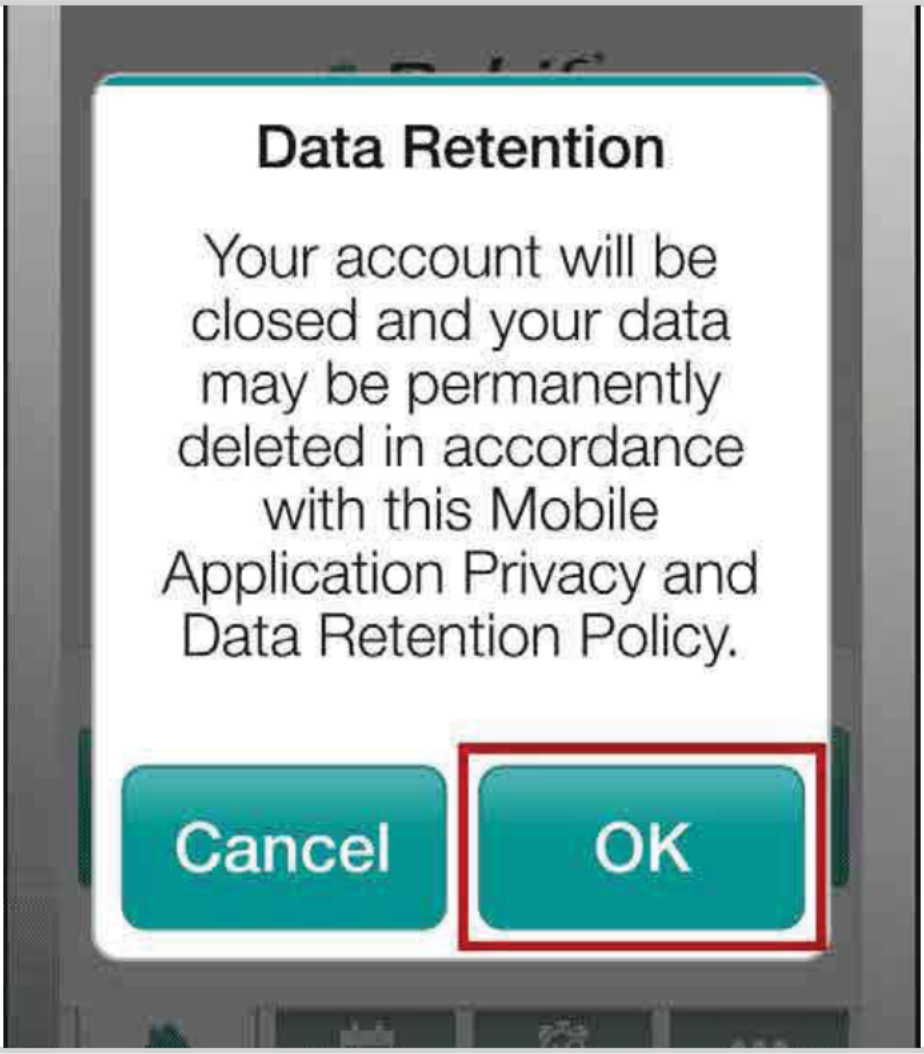


2. Tap Close Account. The Close Account window will appear.

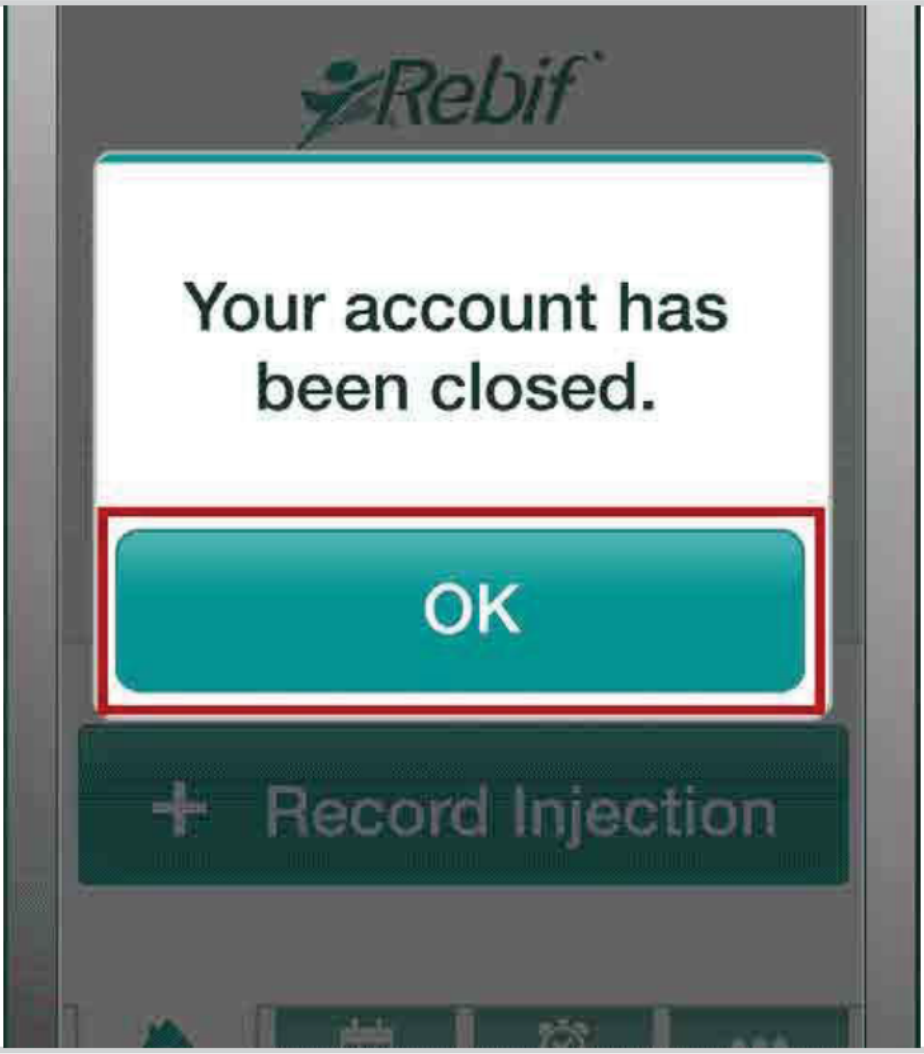
Reference ID: 3991333



3. Tap the Yes button to apply the closure of your account. The Data Retention window will appear.



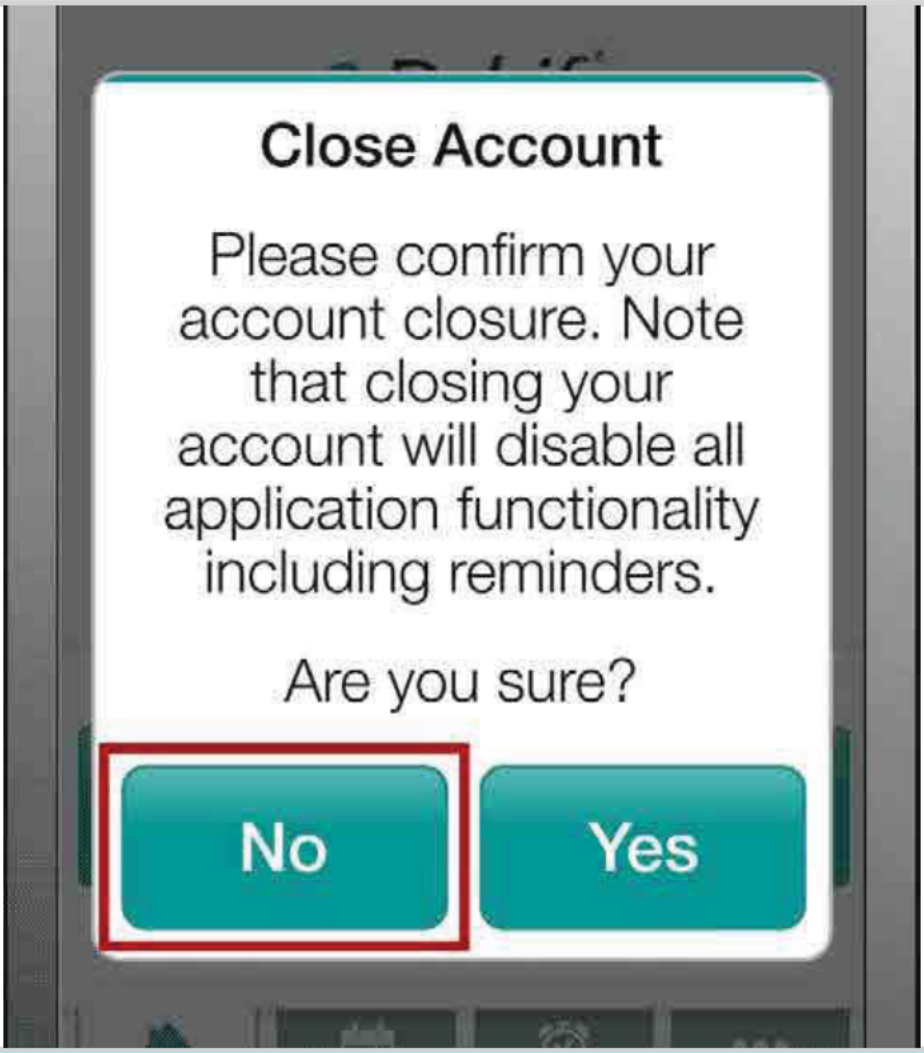
4. Tap the OK button to close the window. The account closure confirmation window will appear.



5. Tap the OK button to close the window. Your account is now succesfully closed.

Reference ID: 3991333

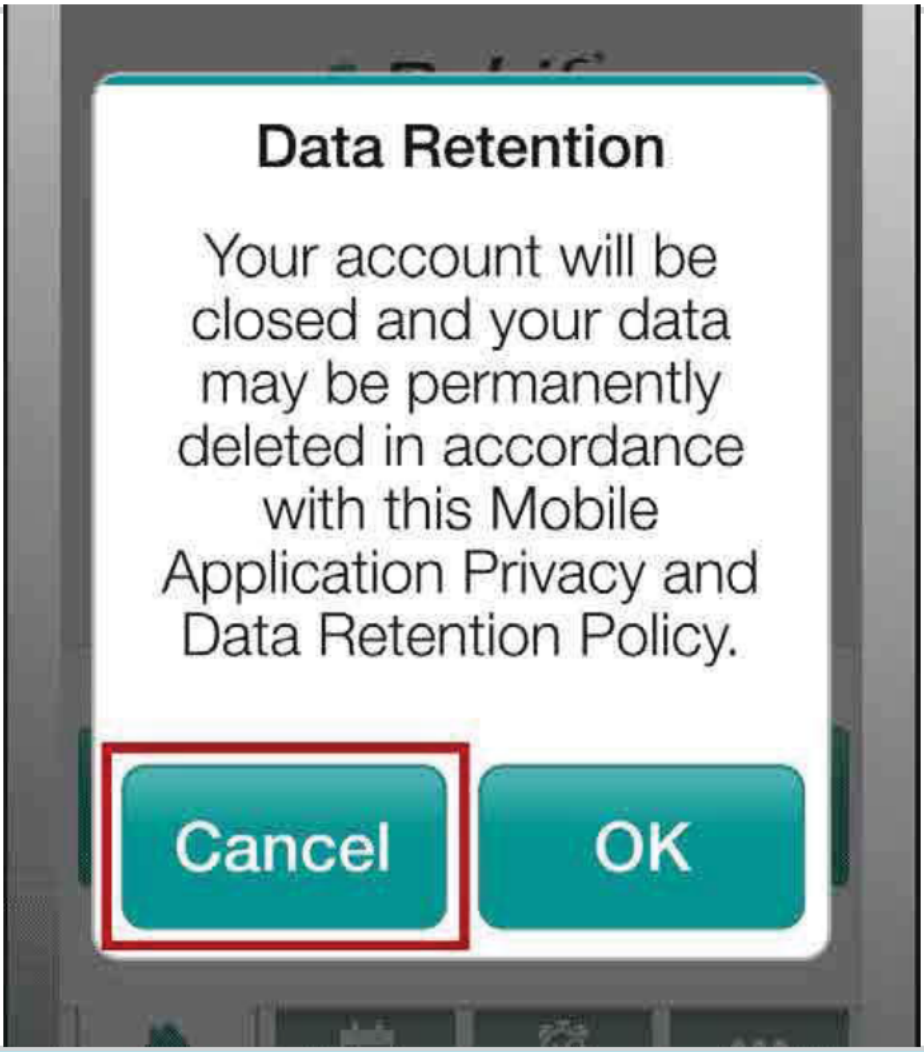
More Tab
Close your Account



NOTE:

To return to the My Account screen without closing your account, tap the No button.

More Tab
Close your Account



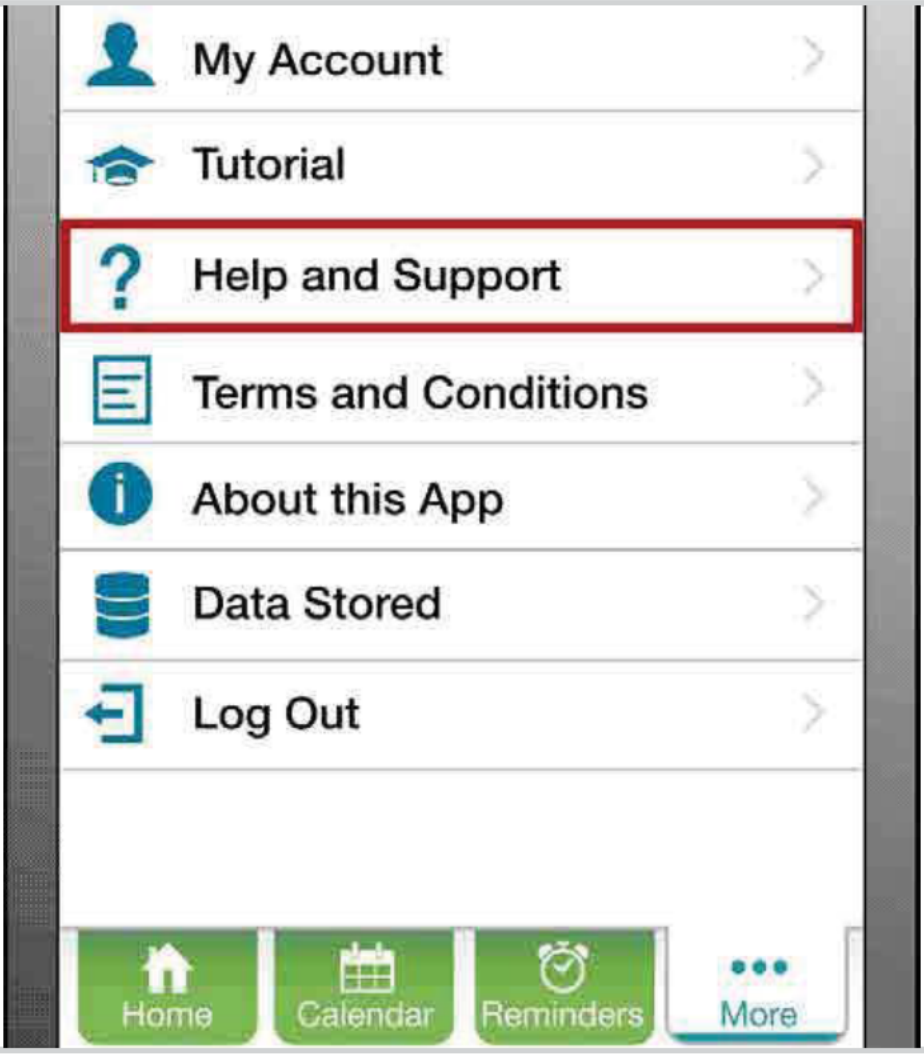
NOTE:

To return to the My Account screen without closing your account, tap the Cancel button.

NOTE:

Your account information remains stored on the server after you close your account. To reactivate your account you need to log in again with your old credentials and follow on-screen instructions, or, contact EMD Serono support.

More Tab
Help and Support



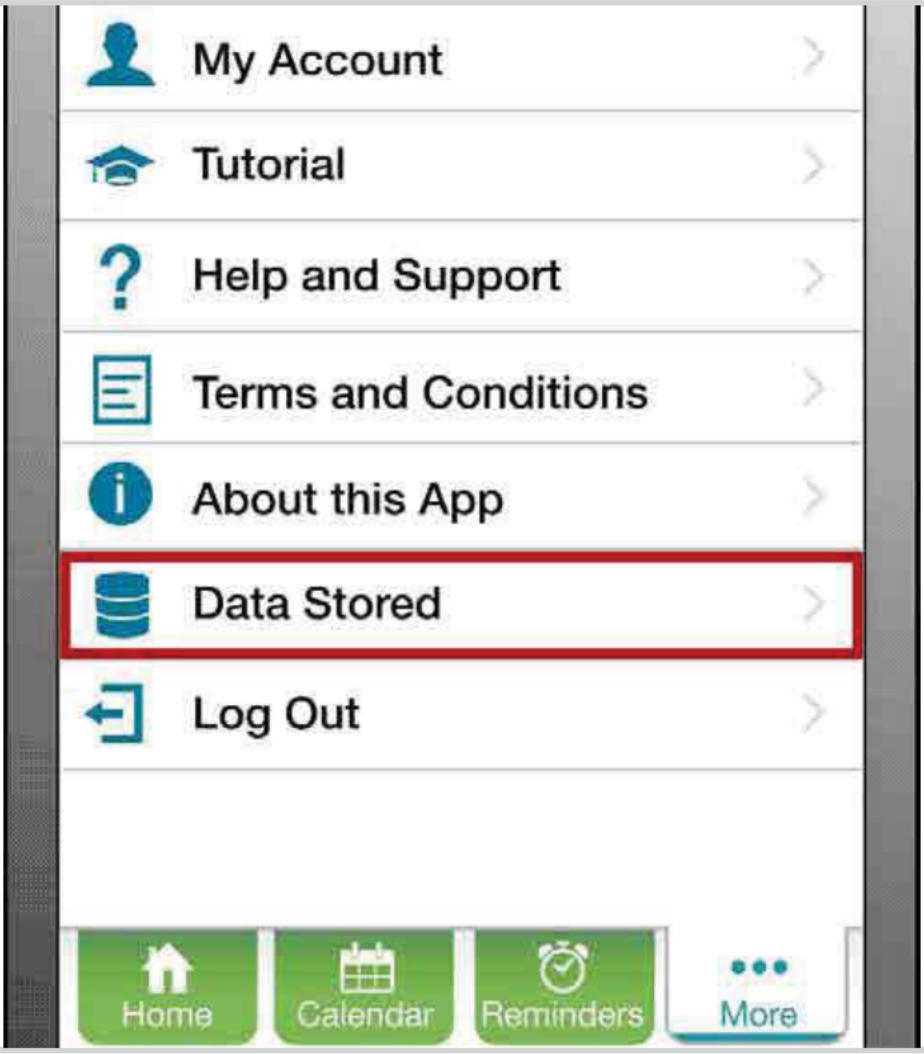
Tapping Help and Support on the More screen will show the Help and Support screen with your support contacts and information about MSdialog™.

Tap the related options on the Help and Support screen to access the following information:

- Support contact information, and information about the MSdialog™ Mobile Application version you are using.
- An electronic copy of the Instructions for Use.
- An electronic copy of the privacy & cookie policy.
- Frequently Asked Questions.

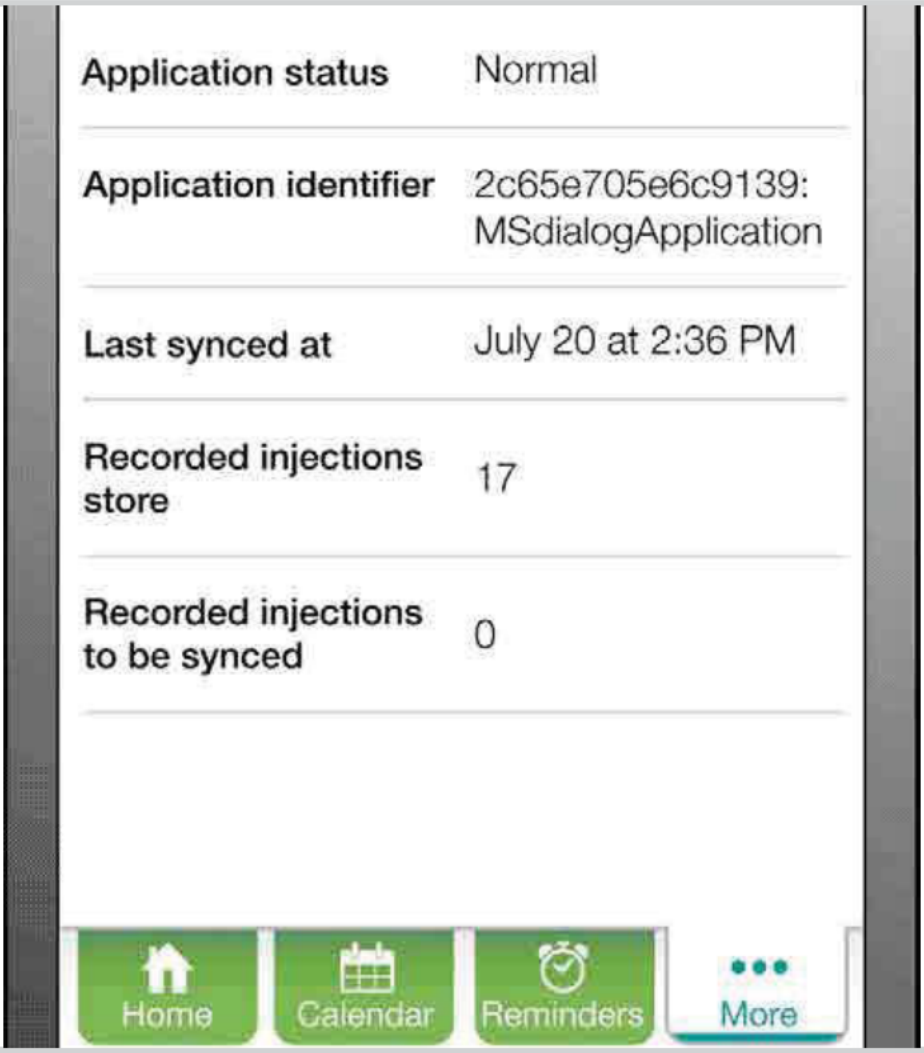
Reference ID: 3991333

More Tab
Data Stored



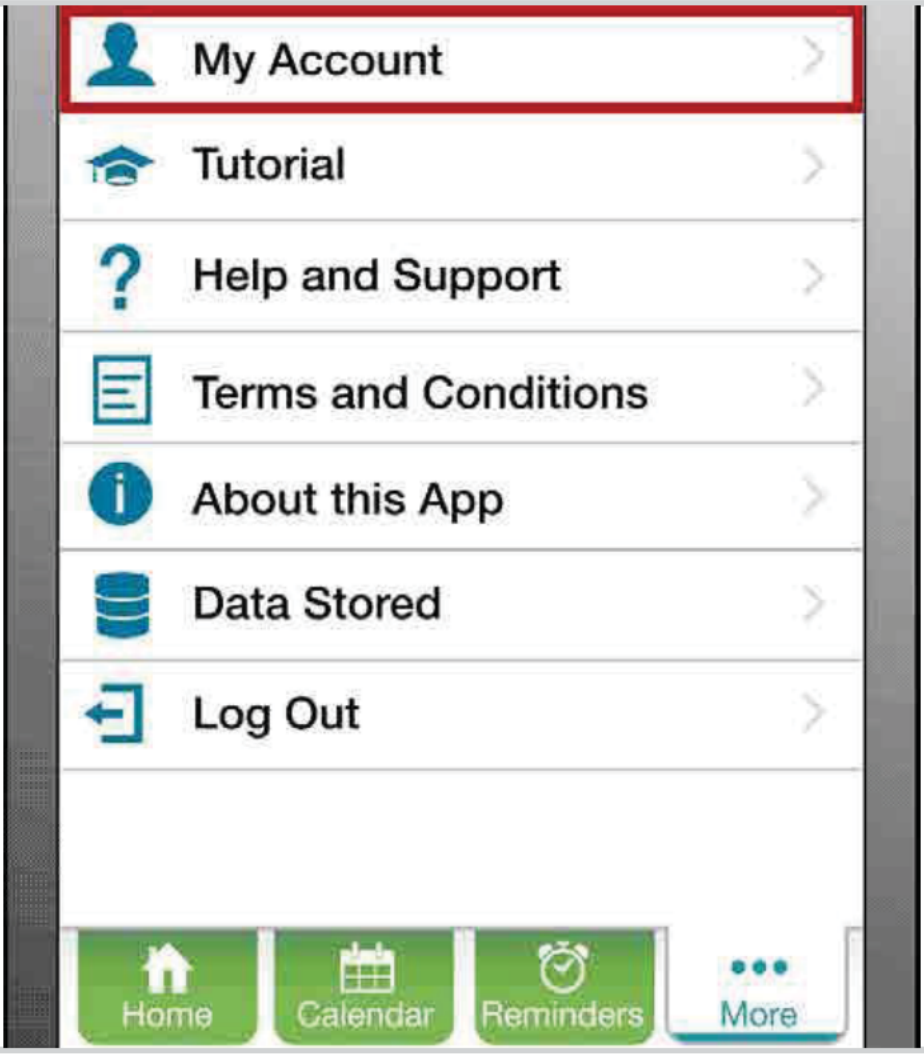
1. Tap Data Stored on the More screen. The Data Stored screen will appear.

More Tab
Data Stored

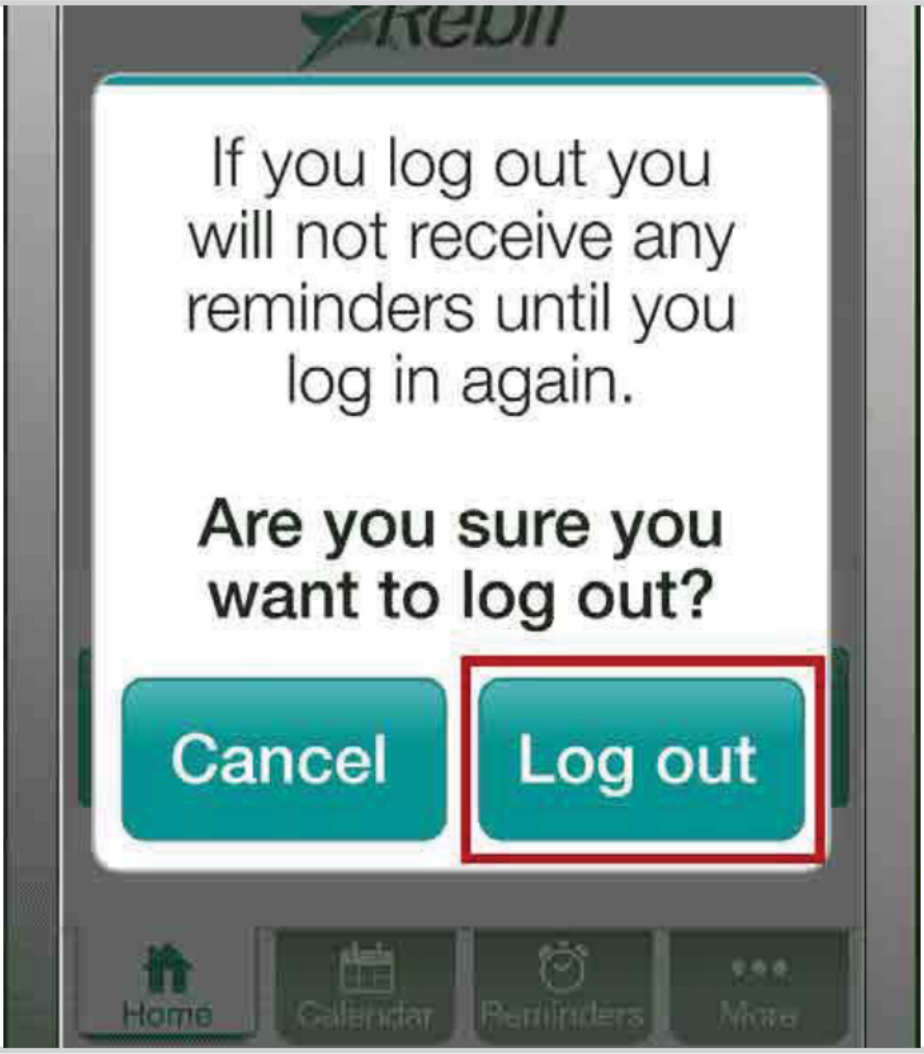


2. This is a repository for persistent data collection, containing your smartphone app status, your last synchronization date, and your medication records.

More Tab
Log Out from MSdialog™



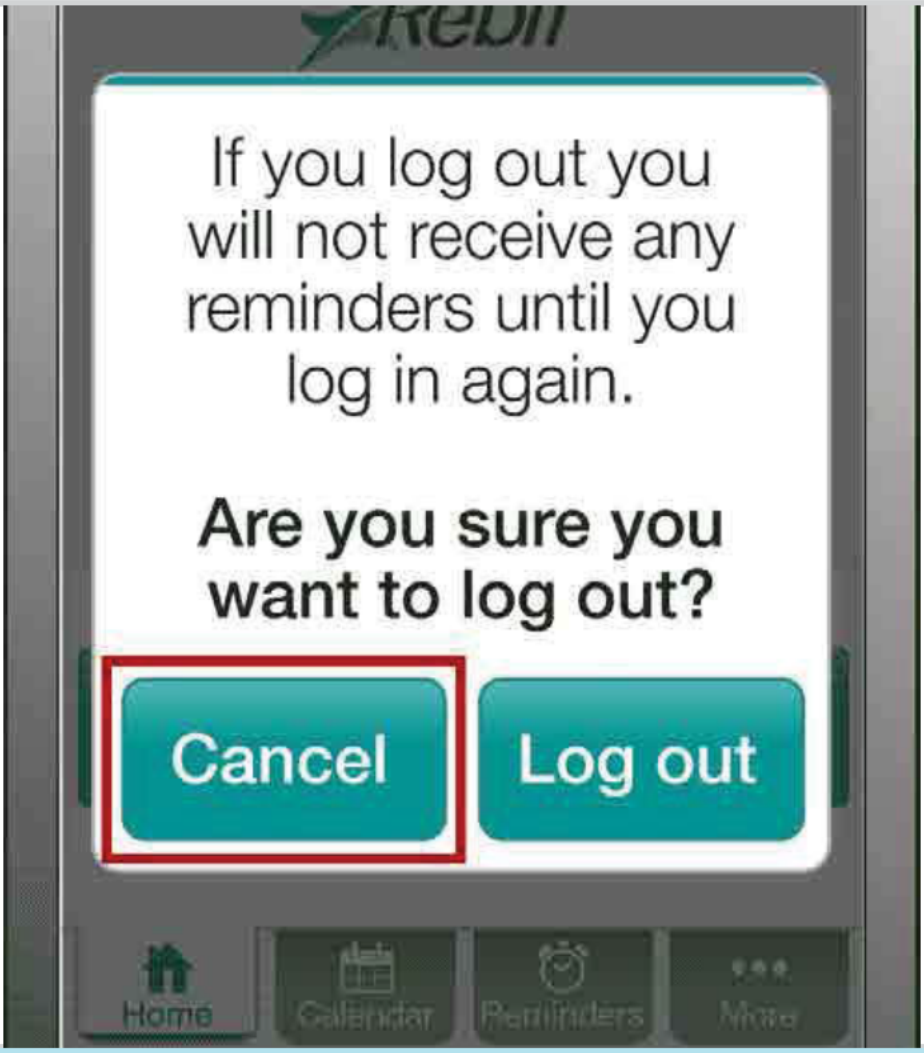
1. Tap Log Out on the More screen. The Confirmation window will appear.



2. Tap the Log out button to log out.

Reference ID: 3991333

More Tab
Log Out from MSdialog™



NOTE:

To return to My account screen without logging out, tap the Cancel button.

Reference ID: 3991333

Reference ID: 3991333

Frequently Asked Questions
Table of Contents

Frequently Asked Questions
Table of Contents

How do I record an injection?

From the Home tab, select the Record Injection button. You will be able to select the injection site or modify the injection time and then confirm your choice by tapping it.

How do I see if I recorded an injection?

On the Calendar tab, look on the displayed calendar for the specific date of interest. If it shows the Normal icon, then an injection was recorded.

Can I delete an injection?

The Mobile App will not allow you to delete injections.

What is the 2D code?

The 2D Code is a symbol similar to this one: 

This black and white symbol will be on your autoinjector label and contains information about your product code, expiration date and lot number.

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What is the NFC tag?

The NFC tag is a chip that stores information about product code, expiration date and lot number. It could be embedded in the label of your autoinjector under the 2D Code.

How do I read the 2D Code on the autoinjector label?

From the Home tab, select the Record Injection button. Using your mobile phone's camera, point the camera at the 2D Code on the autoinjector until the App scans it automatically.

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How do I scan the NFC tag on the autoinjector label? From the HOME tab, select the Record Injection button and you should see an image showing you how to scan the NFC tag. Follow the on-screen instructions until the App scans the NFC tag embedded in the label.

You can also scan the NFC tag on your injector's label by placing your phone's back side next to the autoinjector label until the App scans it.

Why do I need to record injections?

Tracking your injections will help keep a record for future discussions with your healthcare provider.

How can I see if I followed my prescribed treatment schedule?

The Calendar allows you to see if you followed your schedule by showing Normal, Missed and Planned injections.

If you follow your therapy correctly, you should not see any Missed injections. For each

Normal record, you can touch it in the Calendar view to verify it was taken according to your prescribed treatment schedule.

Will I be able to see if I missed an Injection?

Yes, missed injections are shown in the calendar with the ⊗ icon.

How can I see the details of a recorded injection?

The details of each injection can be seen by selecting the day of the injection.

Why does my calendar show this Ⓣ icon?

If you configured your App to use titration, it will mark your recorded injections with the titration icon (Ⓣ). If you are on Rebif® and you are at the beginning of your treatment you might have been prescribed a Titration period where you would start your medication with 6 injections at 20% followed by 6 injections at 50% of the full prescribed dose.

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Why does my calendar show this M icon?

The Multiple injection icon is shown when two or more injections are recorded during the same calendar day.

How can I set my reminder schedule?

On the Reminders tab, select Edit to turn the Reminders feature ON, to set the days of your injection, the Injection Reminder, the medication Dose and the Snooze interval. To save your changes, you need to

confirm your option selecting the Confirm button.

When will I be reminded if I'm traveling through different time zones?

The reminders follow the behavior of your smartphone when traveling between different time zones.

For example, an 8pm reminder in NY on the East Coast would go off at 5pm if you travel to LA on the West Coast.

NOTE:

Do not manually set your phone's current time to your travel destination's future time. Doing so might prevent the MSdialog™ Mobile Application from saving injection data because the application does not allow the recording of future injections.

Do I receive reminders if I log-out?

No, reminders are meant to be personal and are not received if you log-out of the App.

What does the MSdialog™ Mobile Application do?

The App is meant to be used as a medication reminder and diary. It helps you self-manage your treatment schedule, get reminders, and to track your injection history.

The App is not intended to replace the care provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment.

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How do I get started?

The App is simple to use. Make sure you have your Reminders set according to your needs and just follow the on-screen instruction and prompts.

How do I get help on the App?

Select the More tab and you can access the Help and Support menu.

How do I know when there's a new App version?

When a new App version is available, a notice will appear on the App.

Can I use the App on my new phone?

Yes, once you install the App on your new phone, you can migrate your Account by following the on-screen instructions.

NOTE:

Before installing the app on a new phone, on your old phone tap Data Stored on the More screen and verify that Recorded injections to be synced is 0.

I lost my phone, did I lose my data too?

No, if you lose your phone, your data is still available to be downloaded on a new phone.

Can I use the App over two smartphones at the same time?

No, the App can be used only on one phone at a time.

Can I use the App if I do not have data connectivity?

Yes, most of the App's functionality can be used even if you do not have data connectivity.

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Can I change my email in my profile?

Yes. Select the More tab, select My Account, then select Change Email and follow the on-screen instructions.

Can I change my profile?

Yes, select the More tab, select My Account menu and then you can change your email, password and other profile details by selecting the available menus.

Can I close my account?

Yes, you can close your account by going to the More tab, select My Account, then select Close Account and follow the on-screen instructions.

What happens to my data if I close my account?

If you close your account, your data will not be visible or usable by anyone. The details of the data retention policy are shown under the More tab, Terms and Conditions, Privacy policy.

Where is my data stored?

Your data are locally stored on your phone and remotely backed-up on a server in compliance with national security and privacy laws.

Is my data safe and protected from unauthorized use?

Yes, your data are stored on a server in compliance with national security and privacy laws. To further protect your privacy, it is recommended that you use your phone screen PIN lock.

Can I retrieve my username/ password for this Mobile App?

Yes, from the Log In screen, you can select the Forgot email/ password? button and follow the on-screen instructions.

What information is stored by the system?

The App collects the information you enter into it. It stores your profile data and your injection records.

Who can see the information I store in the system?

Your personal identifiable information (Name, email…) can be seen by a trained Care Support Administrator to offer application support. Your personal health information will only be visible by you on the App.

Proprietary Rights, including Copyrights and Trademarks.

This software and documentation contain proprietary information of Ares Trading SA, an Affiliate of Merck KGaA, like EMD Serono. All rights are reserved. Reverse engineering of this software is prohibited. No part of this software or documentation may be copied, photocopied, reproduced, stored in a retrieval system, transmitted in any form or by any means, or translated

into another language without the prior written consent of Ares Trading SA.

EMD Serono and the EMD Serono logo are trademarks or registered trademarks of Merck KGaA. Rebif® and the MSdialog™ logo are trademarks or registered trademarks of Ares Trading SA.

All other names are trademarks or registered trademarks of their respective companies.

Reference ID: 3991333

Contact Information:

EMD Serono, Inc.
One Technology Place
Rockland, MA 02370

MS LifeLines:
1-877-447-3243

ANDROID™ platform
Android Operating System. The operating system software that runs on Android smartphones.

Apple iOS®
The operating system software that runs on Apple iPhones.

MSdialog™ Mobile Application
Smartphone application software that provides patients with easily accessible information to self-manage their treatment.

Reference ID: 3991333

REBIF®

Rebif® is a brand name for a product called interferon beta-1a, which is a medication used to treat relapsing forms of multiple sclerosis (MS).

See the Full Prescribing Information for information about Rebif, including risks associated with the drug such as suicide and depression, hepatic injury, and injection site reactions.

Reference ID: 3991333

Document Conventions

The recommended layout or orientation for using MSdialog™ Mobile Application is portrait; therefore, all screen samples have been captured in this orientation.

This document uses various text formatting conventions to help you identify special terms and notes easily. The following list describes these conventions and provides examples of their use.

- A bold typeface indicates references to buttons and fields in the App.

Reference ID: 3991333

Document Conventions

- A numbered list is used to present an ordered list of steps.
- A bulleted list is used for an unordered series of concepts, items, or options.
- A red outlined rectangle is used to draw attention to a specific area in the user interface.
- Alert icons⚠ indicate important precaution(s) that you must take in using the software.

Reference ID: 3991333

Disclaimer of Warranties

The MSdialog™ Mobile Application, including any Software Updates and Service Releases, is standalone software provided solely for the intended use to help patients manage their treatment schedule.

User expressly acknowledges and agrees that User is solely responsible for use of the software in general. User assumes entire risk as to the installation, accuracy and use of the software, including obtention of any authorizations

and consents required by User for installation and use of the software. In particular, Ares Trading SA does not warrant that installation and operation of the software will be uninterrupted or error-free or that defects in software will be corrected.

User shall assume the entire cost of all necessary equipment (hardware, third party software, internet access, etc.) for the installation and use of the software, including any servicing

or repair arising out of or in connection with such installation or use.

In addition, all terms and conditions of the Software License Agreement apply. By using this Software, you are agreeing to be bound by the terms of this license.

Reference ID: 3991333

Distributor Information

Distributor:

EMD Serono, Inc.
One Technology Place
Rockland, MA 02370 USA

EMD Serono, Inc. is a subsidiary of Merck KGaA, Darmstadt, Germany.

To order a printed version of this instruction manual, please call US Quality Assurance Technical/ Product Complaint Reporting.
Tel: 1-800-283-8088 ext. 2020

Reference ID: 3991333

Version control information:

MDT-705_2015_09-USA-v02

PLS number: 20109536

Revision date: 09-2015

Region code: USA

Reference ID: 3991333

(b) (4)

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
22 mcg / 0.5 mL
For subcutaneous injection

MC-1607-2014

Contains:
12 single-use autoinjectors each with a 0.5 mL syringe.
Active ingredient: interferon beta-1a (22 mcg)
inactive ingredients: albumin human (2 mg)
mannitol (22.5 mg), sodium acetate (0.4 mg)
and water for injection.
No preservative.
Rebif® Rebidose® is produced by Ctrl nese hamster ovary cells.
U.S. standard of potency.

10/14

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
22 mcg / 0.5 mL
For subcutaneous injection

NDC 44087-3322-1

Rx only

Attention pharmacist: Each patient is required to receive the enclosed Medication Guide

EMD Serono

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
22 mcg / 0.5 mL
For subcutaneous injection

USA

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
22 mcg / 0.5 mL
For subcutaneous injection

Manufactured by:
EMD Serono, Inc.
Rockland, MA 02370 USA.
U.S. License # 1773

Dose and administration: See Package Insert. Keep out of reach of children.
For Single-Use Only.
Storage: Store refrigerated between 36°F to 46°F (2°C to 8°C). Do not freeze.

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

3 44087 3322 8

EMD

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
22 mcg / 0.5 mL
For subcutaneous injection

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
22 mcg / 0.5 mL
For subcutaneous injection

GTIN:
Exp. d.:
Lot no.:
SN:

Reference ID 3986207

(b) (4)

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
44 mcg / 0.5 mL
For subcutaneous injection

Contains:
12 single-use autoinjectors each with a 0.5 mL syringe.
Active ingredient: interferon beta-1a (44 mcg)
inactive ingredients: albumin human (4 mg),
mannitol (22.5 mg), sodium acetate (0.4 mg)
and water for injection.
No preservative.
Rebif® Rebidose® is produced by Ares Serono S.A.
Aubonne, Switzerland.
U.S. licensed dosing.

10/14

MC-1105-2014

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
44 mcg / 0.5 mL
For subcutaneous injection

NDC 44087-3344-1

12 single-use autoinjectors

Rx only

For subcutaneous injection

Attention pharmacist: Each patient is required to receive the enclosed Medication Guide

EMD Serono

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
44 mcg / 0.5 mL
For subcutaneous injection

USA

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
44 mcg / 0.5 mL
For subcutaneous injection

Manufactured by:
EMD Serono, Inc.
Rockland, MA 02370 USA.

U.S. License # 1773

Dose and administration: See Package Insert. Keep out of reach of children.
For Single-Use Only.

Storage: Store refrigerated between 36°F to 46°F (2°C to 8°C). Do not freeze.

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

3 44087 3344 1 3

EMD

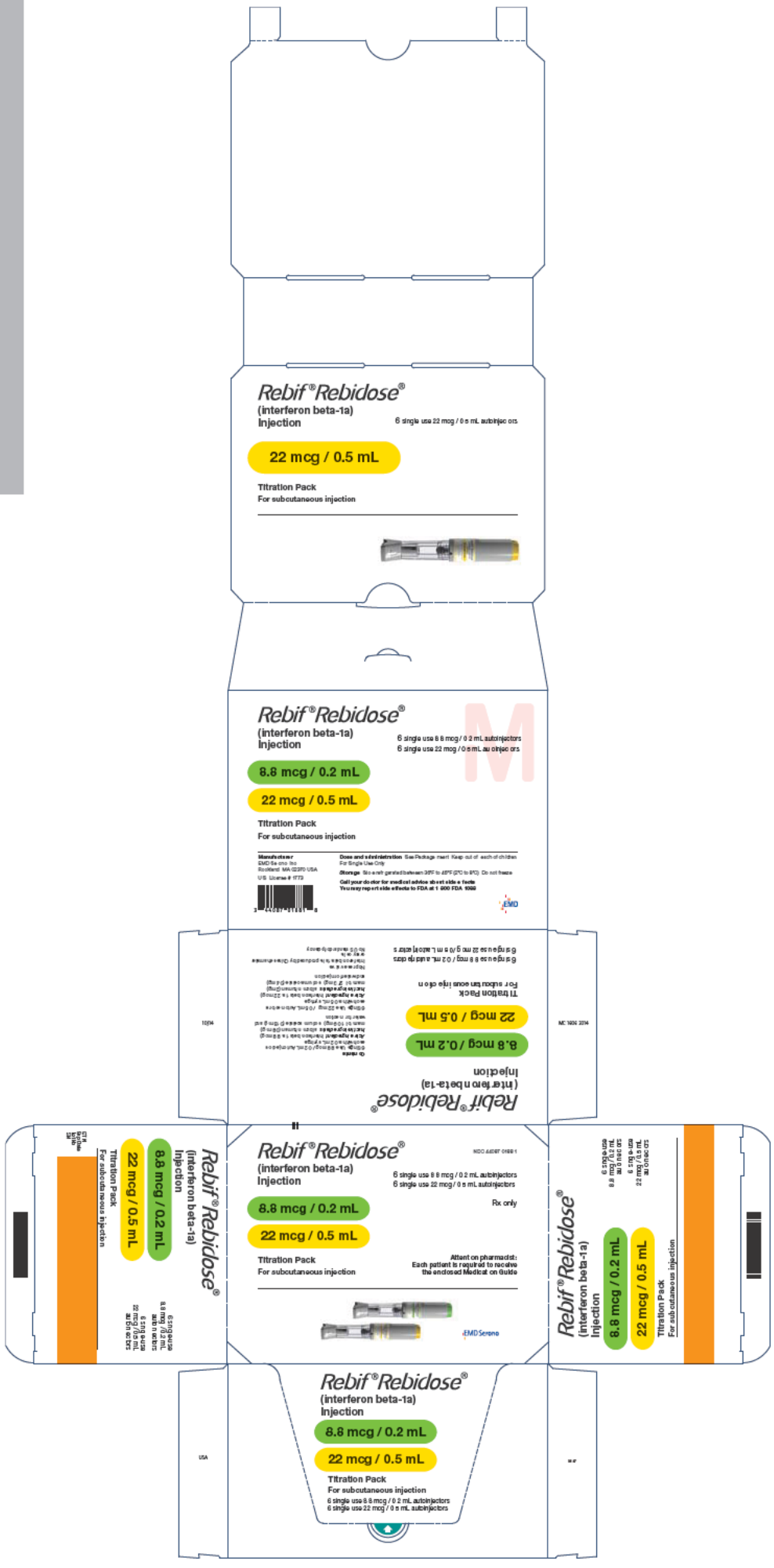
Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
44 mcg / 0.5 mL
For subcutaneous injection

GTIN:
Lot:
Exp:
SN:

Rebif® Rebidose®
(interferon beta-1a)
Injection
12 single-use autoinjectors
44 mcg / 0.5 mL
For subcutaneous injection

Reference ID 3986207

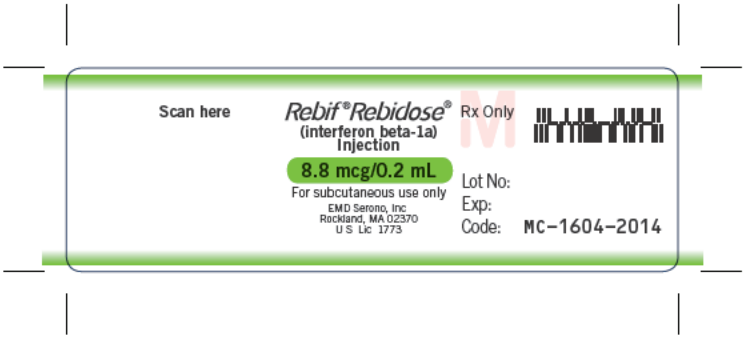
(b) (4)


Rebif® Rebidose®
(interferon beta-1a)
Injection
6 single use 22 mcg / 0.5 mL autoinjectors
22 mcg / 0.5 mL
Titration Pack
For subcutaneous injection
Rebif® Rebidose®
(interferon beta-1a)
Injection
6 single use 8.8 mcg / 0.2 mL autoinjectors
6 single use 22 mcg / 0.5 mL autoinjectors
8.8 mcg / 0.2 mL
22 mcg / 0.5 mL
Titration Pack
For subcutaneous injection
Manufactured by:
EMD Serono Inc.
Rockland, MA 02370 USA
U.S. License # 1773
Dose and administration: See Package Insert. Keep out of reach of children.
For Single Use Only
Storage: Store refrigerated between 36°F to 46°F (2°C to 8°C). Do not freeze.
Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088
EMD Serono
NDC 44087-0188-1
Rx only
Attention pharmacist:
Each patient is required to receive
the enclosed Medication Guide
Titration Pack
For subcutaneous injection
6 single use 8.8 mcg / 0.2 mL autoinjectors
6 single use 22 mcg / 0.5 mL autoinjectors
USA

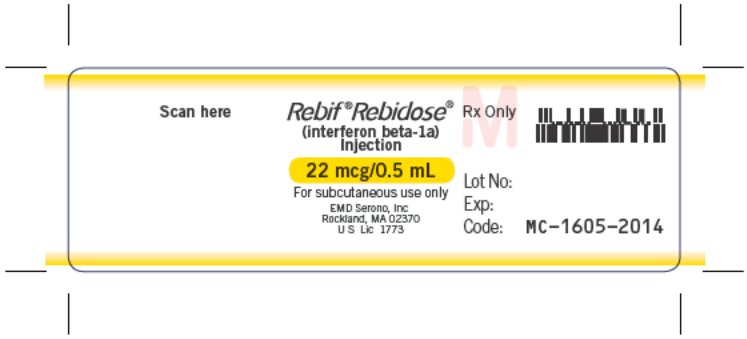
(b) (4)

For more information, please call toll free
1 877 44 REBIF (1 877 447 3243)
Rebif® Rebidose®
(interferon beta-1a)
Injection
Single use 8.8 mcg / 0.2 mL auto injectors
8.8 mcg / 0.2 mL
Titration Pack
For subcutaneous injection

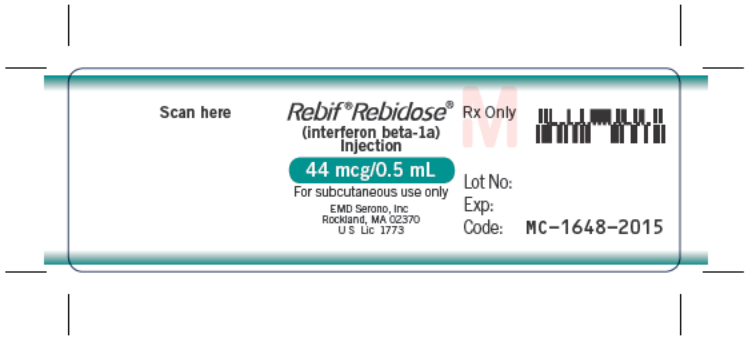
(b) (4)


Scan here
Rebif® Rebidose®
(interferon beta-1a)
Injection
Rx Only
8.8 mcg/0.2 mL
For subcutaneous use only
EMD Serono, Inc.
Rockland, MA 02370
U.S. Lic. 1773
Lot No:
Exp:
Code: MC-1604-2014

(b) (4)


Scan here
Rebif® Rebidose®
(interferon beta-1a)
injection
22 mcg/0.5 mL
For subcutaneous use only
EMD Serono, Inc.
Rockland, MA 02370
U.S. Lic. 1773
Rx Only
Lot No:
Exp:
Code: MC-1605-2014

(b) (4)


Scan here
Rebif® Rebidose®
(interferon beta-1a)
Injection
Rx Only
44 mcg/0.5 mL
For subcutaneous use only
EMD Serono, Inc
Rockland, MA 02370
U.S. Lic. 1773
Lot No:
Exp:
Code: MC-1648-2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103780Orig1s5196

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Eric Bastings, MD. Deputy Director.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	103870 5196
Applicant Name	EMD Serono
Date of Submission	November 27, 2015
PDUFA Goal Date	September 27, 2016
Proprietary Name / Established (USAN) Name	Rebif Rebidose (interferon beta-1b) autoinjector
Dosage Forms / Strength	Subcutaneous injection
Proposed Indication(s)	Relapsing forms of multiple sclerosis
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
OBP Review	Jibril Abdus-Samad and Ralph Bernstein
Office of Prescription Drug Promotion	Aline Moukhtara
CDTL Review	John Marler
CDRH/General Hospital Devices Branch/DAGRID/ODE	Sapana Patel
OSE/DMEPA	Lolita White

OND=Office of New Drugs
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader
OBP=Office of Biotechnology Products
CDRH=Center for Devices and Radiological Health

1. Introduction and Background

The supplement under review proposes to add a 2D barcode and near field communication (NFC) tag to the labeling of the approved Rebif autoinjector (Rebidose). The 2D barcode and NFC tag would embed the lot number, expiry date, and product ID number onto the autoinjector label. This would give patients an option to monitor their use of the Rebidose autoinjector using a smartphone App (Msdialog Mobile Application). The Msdialog Mobile Application allows patients to select a predefined medication schedule, record each injection, and review their compliance with the prescribed injection dose and schedule. The Msdialog Mobile Application also transmits product use data to an web-based software (MSdialog) that can display usage data graphically to the patient and, if the patient consents, to health care professionals (physicians and nurses). Some clinical outcomes and patient-reported outcome tools are also included in the MSdialog web-based software application.

2. CMC/Device/OSE-DMPA

I concur with the conclusions reached by the Office of Biotechnology Products (OBP) reviewers and the device (CDRH) reviewer regarding the acceptability of the proposed changed to the Rebidose autoinjector labeling. The OBP review team concluded that the Applicant provided data that demonstrate that the Rebif drug product is not adversely affected by exposure to the NFC radio frequency electromagnetic emissions. Changes to the carton and container were found acceptable.

The CDRH/device reviewer notes that there were no changes made to the Rebidose device components, or to the assembly process of the autoinjector except to add the new printer/encoder equipment. The reviewer also notes that the Msdialog Mobile Application was developed in accordance with the FDA Final Guidance for Industry on "Mobile Medical Applications", issued on February 9, 2015.

OSE/DMEPA conducted a limited review of the MSdialog web-based software application, as the team concluded that it does not provide clinical decision support features and functionality that are expected to require alteration of physician or caregiver behavior. The DMEPA reviewer also notes that MSdialog web-based software application functions as a tool which only allows for monitoring and communication, and should be technically accurate and meet any required data integrity specifications. In addition, as noted by Dr. Marler, future changes to the MSdialog system that may introduce additional risk could change the level of review needed. (b) (4)

The OSE/DMEPA review of the Msdialog Mobile Application and of the human factors study conducted to support the usability of the Msdialog Mobile Application identified a number of deficiencies, which were all resolved during this review cycle.

There are no outstanding CMC or device/human factors issues.

3. Nonclinical Pharmacology/Toxicology

Not applicable.

4. Clinical Pharmacology/Biopharmaceutics

Not applicable.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

Not applicable.

7. Safety

Not applicable.

8. Advisory Committee Meeting

No advisory committee was necessary for this supplement.

9. Pediatrics

Not applicable.

10. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

11. Labeling

There are no other unresolved relevant regulatory issues.

12. Decision/Action/Risk Benefit Assessment

The Applicant has provided adequate information to support the proposed labeling changes, i.e., adding a 2D barcode and near field communication (NFC) tag to the labeling of the approved Rebif autoinjector (Rebidose), and to support the use of the smartphone application (Msdialog Mobile Application) that will allow patients to track their injections as well as optionally share this information with their healthcare providers and communicate regarding aspects of their treatment. Therefore, I will issue an approval letter for this supplement.

As the MSdialog web-based software application does not provide clinical decision support features and functionality that are expected to require alteration of physician or caregiver behavior, the team conducted a limited review of the web-based software. Because they were not fully reviewed, the Instructions for Use (IFUs) for the MSdialog web-based software application will not be attached to the approval letter.

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

/s/

ERIC P BASTINGS
09/27/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103780Orig1s5196

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review
Division of Neurology Products (DNP)
CDER

Date	September 10, 2016
From	John R. Marler, MD
Subject	Cross-Discipline Team Leader Review
Application Number	BLA 103780 Prior Approval Supplement 5196
Applicant	EMD Serono
Date of Submission	November 27, 2015
PDUFA Goal Date	September 27, 2016
Name Proprietary/ Non-Proprietary	Rebif Rebidose (interferon beta-1b) autoinjector
Dosage form	Subcutaneous injection
Applicant's Proposed Indication	Relapsing forms of multiple sclerosis
Recommended Regulatory Action	Approval
Recommended Indication	REBIF (interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.

1. Background

The applicant proposes to add a 2D barcode and near field communication (NFC) tag to the labeling of the approved Rebif (interferon β-1a) autoinjector called Rebidose. These changes will give patients the option to monitor their use of Rebif using a smartphone to read the lot number, expiration date, and product ID number using a mobile medical application (MSdialog) to track product use rather than a handwritten diary. In turn, the MSdialog smartphone application transmits product use data to an internet application (MSdialog Web) that can display usage data graphically to the patient and, if the patient consents, health care professionals. In addition to the collection and display of the injection data, patients can use MSdialog Web to report their quality of life using patient-reported outcomes (MusiQoL and MSQLI[1]).

The approved doses of Rebif are either 22 mcg or 44 mcg injected subcutaneously three times per week after a 4-week-long introductory titration period. The drug label[2] recommends administration at the same time (preferably in the late afternoon or evening) on the same three days each week (for example, Monday, Wednesday, and Friday) and at least 48 hours apart. Rebif is available in prefilled syringes and single-use Rebidose autoinjectors containing 8.8, 22, or 44 micrograms of interferon β-1a. The drug label does not recommend actions to take if a patient misses a dose.

There is a different titration schedule for each of the two recommended doses (22 or 44 mcg). See Table 1 and Table 2 below.

Table 1 Titration Schedule for 22mcg Prescribed Dose

Week of Use	Dose	Syringe to Use	Amount of syringe
Week 1 Titration	4.4 mcg	8.8 mcg syringe	Use half of syringe
Week 2 Titration	4.4 mcg	8.8 mcg syringe	Use half of syringe
Week 3 Titration	11 mcg	22 mcg syringe	Use half of syringe
Week 4 Titration	11 mcg	22 mcg syringe	Use half of syringe
Week 5 and after	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector

[1] MusiQoL: Multiple Sclerosis International Quality of Life questionnaire. MSQLI: Multiple Sclerosis Quality of Life Inventory.

[2] Rebif label on FDA website revised 10/2015. Other revisions are under review at this time, 7/2016.

*Use only prefilled syringes, not autoinjectors, to titrate to the 22 mcg Prescribed Dose

Table 2 Titration Schedule for 44mcg Prescribed Dose

Week of Use	Dose	Syringe or Autoinjector to Use	Amount of syringe or autoinjector
Week 1 Titration	8.8 mcg	8.8 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 2 Titration	8.8 mcg	8.8 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 3 Titration	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 4 Titration	22 mcg	22 mcg syringe or autoinjector	Use full syringe or autoinjector
Week 5 and after	44 mcg	44 mcg syringe or autoinjector	Use full syringe or autoinjector

**Prefilled syringes or autoinjectors can be used to titrate to the 44 mcg Prescribed Dose

The Disease.

Relapsing multiple sclerosis (RMS) is a chronic progressive brain disorder characterized by episodes of neurological dysfunction, relapses, which generally occur at a rate of once every two years and usually last less than 30 days. Most commonly, *relapses* are episodes of weakness or numbness in an arm or leg, pain and loss of vision in one eye, unsteady walking, double vision, difficulty speaking, or dizziness. Early in the disease course, the relapse symptoms resolve leaving minimal or no disability. The clinical symptoms and rate of worsening are widely variable. In some longitudinal studies, the progression of irreversible disability occurs independently from relapses as if they are two separate aspects of the disease.[3] Generally, the age that symptoms first appear is 20-50 years. Two-thirds of patients are women. Over several years, many, but not all, MS patients experience some degree of persistent disability. Among those who do become disabled, the mean time from first symptoms is 11.4 years until disability becomes significant but leaving the patient self-sufficient and up and about some 12 hours a day and able to walk without aid or rest for 500 meters. The average time is 23.1 years before there is a need for a cane or crutch despite the ability to walk 100 meters.[3] MS shortens lifetimes by about 5 years.

[3] Christian Confavreux, M.D., Sandra Vukusic, M.D., Thibault Moreau, M.D., And Patrice Adeleine, M.D., Relapses And Progression of Disability In Multiple Sclerosis, NEJM, November 16, 2000, No. 20, Volume 343, pp. 1430-8.

Twelve different drugs are FDA-approved to prevent relapses in RMS.[4] Five of the 12 are interferon β-1 (a or b) products. All of the drugs reduce relapse rates. Rebif is superiority to another interferon β-1a, Avonex, for reducing the proportion of relapse-free patients at 2 years. In general, evidence of an effect on relapse rate is stronger than evidence of an effect on disability progression during the two-year exposure in most RMS trials: the evidence in RMS drug labels for a reduction in disability progression shows smaller effect sizes and lacks confirmation in a second trial for some drugs.[5]

The Drug

The Rebif drug substance is interferon β-1a. The Rebif prescribing information describes a 29 to 32 percent reduction in the number of relapses per year compared to placebo on two studies and a reduction in patients with disability progression sustained for 3 months in 8 to 11 percent of patients.

2. Product Quality

Ralph M. Bernstein evaluated the stability of the Rebif drug product after exposure to the radio frequency electromagnetic radiation (RFEM) used to scan the 2D Matrix Code or NFC chip with a cell phone or other related RFEM scanning devices. The 2D Matrix code is printed on the carton and the NFC chip is embedded in the carton below the printed 2D Matrix Code. See Figure 1 and Figure 2. He recommends approval because the applicant provided data that demonstrate that RFEM does not adversely affect the Rebif drug product.

[4] Betaseron, Avonex, Copaxone, Rebif, Tysabri, Gilenya, Aubagio, Tecfidera, Plegridy, Lemtrada, Daclizumab, and Novantrone. Extavia is Betaseron under another name and Glatopa is a generic form of Copaxone.

[5] **Error! Reference source not found.**, Appendix, page 48

Figure 1 Carton Label with NFD and 2D Matrix Code

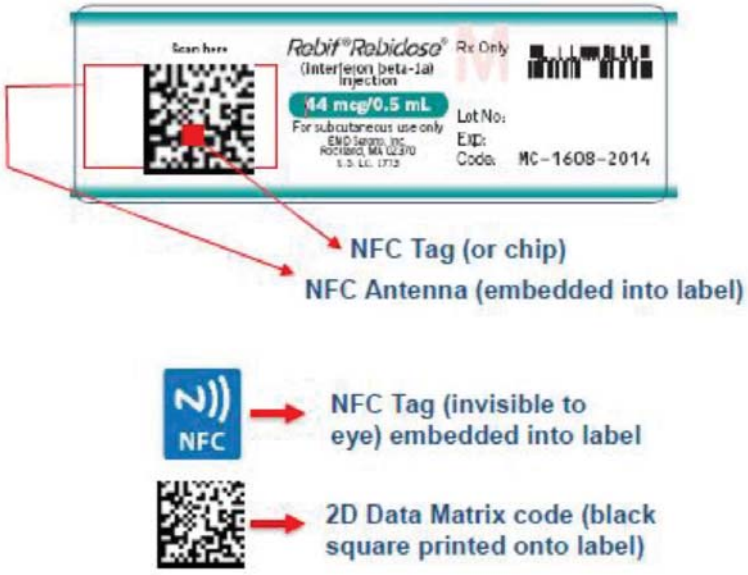


Figure 2 Rebidose Autoinjectors for 8.8, 22, and 44 mcg.

3. Device Review

Sapana Patel, PharmD, General Hospital Devices, CDRH, wrote the primary review of the device. Consultants were Patricia Beaston, M.D., Ph.D., Medical Officer, Lening Shen, Software Review, Brian Fitzgerald, Cybersecurity Review, and Seth Seidman, Radiofrequency Review.

CDRH recommends approval of the device and associated applications (MSdialog and MSdialog Web) pending updated labeling, which has been received from the Applicant after filing of the CDRH review (CDRH recommended that labeling made no claim that the Mobile App [redacted] (b) (4) to an injection log, and that the Mobile App Instructions for Use state that the Mobile App is only for use by patients prescribed Rebif based on the FDA-approved prescribing information).

The review of the device concluded that

1. The assembly and shipping of the final finished product have no affect on the functional integrity of the proposed new label
2. Exposure to radio frequency electromagnetic (RFEM) emissions does not affect the critical quality attributes and stability of the drug product
3. RFEM does not change the physico-chemical properties of the device.

The CDRH reviewers were concerned that the instructions for use (IFU) for both Apps (mobile and web) state that they are used as a tool to (b) (4). CDRH recommended that the related IFUs state that (b) (4) the applications assist with keeping records of injections. The concern with the Applicant claiming that the Apps (b) (4) In response to CDRH recommendations, appropriate changes were made to the IFU for both Apps during the review process.

The Applicant provided a comparability protocol for the MSdialog System software. The comparability protocol was reviewed by CDRH and DMEPA; changes requested by both groups were incorporated by the Applicant.

In addition, CDRH recommend that the clinical team considers the acceptability of a proposed 2-hour variation around the recommended 48-hour minimum time between injections, and of not readjusting dose reminders in the case of injections that may have been taken off schedule. These issues were discussed, and do not raise clinical concerns.

4. DMEPA Review

Lolita White, PharmD, performed the primary reviewer for the Division of Medication Error Prevention and Analysis (DMEPA). Quynh Nhu Nguyen, MS, is the Associate Director for Human Factors; Irene Z. Chan, PharmD, BCPS, is the DMEPA Deputy Director.

The DMEPA review concludes that EMD Serono has submitted sufficient evidence to determine that the user interface supports the safe and effective use of the Rebif product and MSdialog system.

In their review of the supplement application, DMEPA determined that the MSdialog Web Apps do not provide clinical decision support features and functionality that would require alteration of physician or caregiver behavior. Hence, DMEPA focused their evaluation on the human factor (HF) study results for the MSdialog Mobile Application. In their review, DMEPA identified issues with the IFUs for both

applications. In response to information requests, the sponsor has resolved these issues with modifications to the IFUs.

5. Other Relevant Regulatory Issues

FDA's review of the MSdialog Web Apps was limited given the low potential risk to patients associated with the Apps' current functionality. However, future changes to the MSdialog System that may introduce additional risk could change the level of review needed. (b) (4) Therefore, the approval letter will explain that we limited our review of the MSdialog Web App because of the low risk and advise the applicant that future changes could require a more in-depth review.

6. Labeling

The sponsor made numerous changes to the IFUs for the MSdialog System in response to FDA requests. FDA did not fully review the IFUs for the MSdialog Web application because, after an initial evaluation, DMEPA determined that this application does not provide clinical decision support features and functionality that would require alteration of physician or caregiver behavior. Because they were not fully reviewed, the IFUs for the MSdialog Web applications will not be attached to the approval letter.

7. Postmarketing Recommendations

None.

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/s/

JOHN R MARLER
09/27/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103780Orig1s5196

CHEMISTRY REVIEW(S)

MEMORANDUM
Through: Cris Ausin, Team Leader DBRR IV, OPQ, CDER
From: Ralph M. Bernstein, DBRR IV.
Date: 28 July 2016
Re: PAS 5196/eCTD series 0213 IR Response 0217. The addition of a new label to the Rebif PFS autoinjector SUAI (Rebidose) that contains a 2D bar code and an "invisible to the eye" near field communication tag (NFC).
Product: IFN-β Rebif BLA#103780 as indicated for RRMS.
Presentation: Each 0.5 ml (0.5 cc) of Rebif® contains either 44 mcg, 22 mcg or 8.8mcg of interferon beta-1a, 4 or 2 mg albumin (human) USP, 27.3 mg mannitol USP, 0.4 mg sodium acetate, Water for Injection USP. Rebidose is an SUAI that contains the Rebif PFS.

Purpose: the purpose of this review is to evaluate the CMC only component of the PAS. In this case, the CMC component is the stability of Rebif DP after exposure to radio frequency electromagnetic radiation (RFEM), that Rebif DP could theoretically be exposed to when the 2D label or NFC chip is scanned by a cell phone or other related RFEM scanning devices. Labeling, computer software compliance, NFC and bar code integrity, and clinical components for this supplement will be evaluated in other parts of CDER and CDRH.

Manufacturer: EMD Serono, MA, USA (in Europe, referred to as Merck KGaA, Frankfurter Str. 250, D-64293 Darmstadt, Germany).

Abbreviations:
CMC chemistry manufacturing and controls, i.e., product quality
DP: drug product
IR information request
NFC near field communication
PFS: pre filled syringe
Rebif: Rebif is the name of the licensed drug product. It is filled into a PFS. The identical PFS is used in each Rebidose SUAI.
Rebidose: the trade name of Rebif encapusulated within a SUAI.
RFEM radio frequency electromagnetic radiation

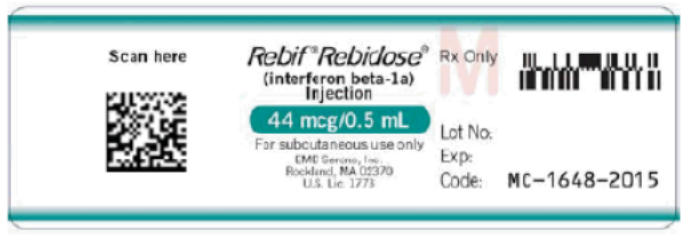
RRMS relapsing remitting multiple sclerosis
SUAI single use autoinjector

Submitted: 25 Nov 2015
Quality IR Response received: 19 Feb 2016

Recommendation:
I recommend that from a CMC/quality perspective, this PAS is approvable. The Sponsor has provided data that demonstrate that Rebif DP is not adversely affected by exposure to RFEM in studies representing real time/real world exposure.

Background:
EMD Serono submitted a PAS on 25 Nov 2015 to allow the change in labeling of the SUAI Rebif, known as Rebidose, to include a label with a 2D barcode and a NFC tag for administration tracking purposes. See proposed label, below:

Figure 1: Representative 44 mcg Rebif® Rebidose® Proposed Label Design



FRONT SIDE

(b) (4)

The new labels allow for tracking by virtue of either being scanned by a smartphone or other QR code compatible device, or to be scanned with an NFC compatible detector. Both modes of scanning theoretically expose the Rebif IFNβ DP to RFEM. See Figure 1, below, of label placed on to the SUAI.

Figure 1: Rebif Rebidose Label Change Proposed

See Figure 2, below, for cartoon depiction of tracking the Rebif Rebidose SUAI prior to use.

Figure 2: Rebif Rebidose IFU pages 16-17

Recording your injections (continued)

Choose one of the following two options:

Option 1: Scan 2D code

1) Point the smartphone's camera at the auto-injector's label, centering the 2D code in the application's viewing window.

2) Hold the smartphone steady until it makes a sound or vibrates, indicating that the 2D code has been scanned.

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Option 2: Read NFC tag

1) Hold the NFC tag against the back of the smartphone, making sure the label contacts the smartphone's back.

2) Hold the smartphone steady until it makes a sound or vibrates, indicating that the NFC tag has been read.

17

(b) (4)

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/s/

RALPH M BERNSTEIN
07/28/2016

CRISTINA AUSIN-MORENO
07/28/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103780Orig1s5196

OTHER REVIEW(S)

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:	September 20, 2016
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 103780/s5196
Product Name and Strength:	MSdialog Mobile Application
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	EMD Serono, Inc.
Submission Date:	November 27, 2015
OSE RCM #:	2015-2767
DMEPA Primary Reviewer:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

EMD Serono has submitted a prior approval supplement (S-5196) to introduce the MSdialog System, a system that was created to provide a tracking and medication reminder tool for patients with Relapsing Multiple Sclerosis (RMS) who are prescribed Rebif® Rebidose® Autoinjector (AI). The system allows patients to track their injections as well as optionally share this information with their healthcare providers and communicate regarding aspects of their treatment.

The Division of Neurology Products (DNP) consulted DMEPA to review the proposed revisions to the labels and labeling as well as the human factors validation study (HFS) results for the MSdialog Mobile Application submitted to the agency on November 27, 2015.

2 BACKGROUND

The MSdialog system includes three components: (1) Rebif Rebidose autoinjector with a "smart" label, (2) the MSdialog Mobile Application, and (3) the MSdialog Web Applications. The MSdialog Mobile App records injections taken by the patient either via manual input or by electronically reading the "smart" label on the Rebidose (a user can scan the Rebif® Rebidose® Autoinjector smart label according to directions in the autoinjector's instructions for use (IFU)). When the patient's smart phone has internet access, the recorded data will be synchronized with the MSdialog Web Applications (Apps) via a secure internet connection. The MSdialog Web Apps are internet-based software applications that have dedicated user interfaces for patients, field nurses, and healthcare providers (HCPs). The web apps were developed to (b) (4) (b) (4) provide secure web-based platforms for HCPs, field nurses, and patients to record and share information on aspects of treatment. At this time, we have determined that the MSdialog Web Apps do not provide clinical decision support features and functionality that are expected to require alteration of physician or caregiver behavior. Additionally, other than responding to questionnaires provided by a healthcare provider, there is no other data entry requirement for patients. Based on EMD Serono's description of the web apps, they function as tools which only allow for monitoring and communication, and should be technically accurate and meet any required data integrity specifications. Thus, we focus our evaluation in this review on the HF study results for the MSdialog Mobile Application (hereafter referred to as 'app') utilized by patients that will require interacting with the app and taking appropriate action in response to alerts and instructions.

3 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

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	n/a
FDA Adverse Event Reporting System (FAERS)*	n/a
Other-Summative Human Factors Validation Study Results, Summative Human Factors Validation Study Protocol, MSdialog Human Factors Risk Management Report	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

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sections below discuss our key findings from our evaluation of EMD Serono's submitted materials:

Autoinjector Label

We reviewed the modified Rebif® Rebidose® AI "smart" label for risk of medication error. The AI label has been revised to add a 2D barcode (Data Matrix) and a Near Field Communication (NFC) tag that does not exist for the currently marketed product. The proprietary name, dosage form, route and other critical identifying information on the device label remains unchanged. We find that the 2D barcode is located in a space with adequate white area to optimize scanning and the NFC tag is placed such that it does not obscure prominent information. We have no recommendations for the AI label.

Carton labeling

We note that the carton labeling, which contains the revised Rebif® Rebidose® AI with "smart" label, does not specifically identify the contents as such or make reference to the MSdialog system. During a prior face-to-face meeting with EMD Serono held on October 2, 2015, the Agency was informed that there will be an estimated twelve week transition period where both versions of the AI labels will be circulating in the market. EMD Serono intends to replace the currently marketed Rebif® Rebidose® AI with the revised version once approved and will not continue to market both versions

simultaneously. We considered the risk for adverse events if a patient were to receive the wrong version of the AI; however, we note that the patient will be able to manually enter in their injection data into the MSdialog mobile app as scanning is not required to use the system, and there is no risk for clinical harm. Given the limited time for overlap on the market and the lack of harm, we do not recommend further changes to the carton labeling at this time.

Human Factors Validation Study for the MSdialog mobile app

The first time a patient uses the MSdialog mobile app they must first complete registration. During the validation study, after completing registration, some study participants were exploring the app and accidentally recorded injections without actually administering injections. These participants stated that they believed they could erase the documentation later since they were only exploring the app. To minimize the risk for faulty documentation of injections that do not take place, EMD Serono updated the mobile app. During registration of the product, users are required to view a tutorial in the mobile app. As part of the tutorial, a warning note was added stating that "recorded injections cannot be deleted." We note that this change was not validated with further HF testing. We are concerned that this change to the tutorial may not be adequate to minimize the risk for this type of failure. We recommend that a similar warning is placed on the screen when a patient begins to record an injection so that the warning is reinforced and the patient knows before they begin recording an injection that what is entered cannot be deleted.

The HF validation study identified failures with correctly setting the injection reminders, both during initial registration as well as when testing how to change reminder times. These are considered critical tasks. According to EMD Serono, during the registration process patients are instructed by the electronic IFU embedded within the mobile app to enter the medication settings as prescribed by their HCP as well as their injection reminder preferences (reminders on/off, and amount of snooze time). The reminder time will always default to the time entered for the patient's injection time. To change the reminder time, patients much also change their set injection time. During the validation study, patients were given user profiles with injections times that they were required to enter; however, because the patients were current Rebif users, instead of entering the times given to them as part of the use scenario, they entered the times that they would normally inject at home. Thus, we have determined that the failures can be attributed to study artifact. We note that some participants stated that there was no warning or additional screen requiring a patient to confirm that the injection time entered is correct; however, this is unlikely to have prevented these failures during

the validation study as the underlying problem can be tied to confirmation bias due to the participant's own injection schedule with Rebif. We find the residual risk acceptable and do not recommend any changes at this time to address these failures.

During the record injection sequence, one participant read the [redacted] (b) (4) warning and thought she was [redacted] (b) (4) scheduled injection regimen rather than [redacted] (b) (4) injection recording. The root cause for this was reported to be the ambiguous wording as it does not clearly tell you what you are [redacted] (b) (4). EMD Serono did not propose any mitigations because they determined the risk to be low with no patient safety-related harm anticipated. We recommend the [redacted] (b) (4) warning be clearly labeled to include exactly [redacted] (b) (4) in order to decrease risk of confusion.

We note during the HF validation study, some participants did not scan the AI 2D code/NFC tag ("smart" label) when recording an injection and switched to the manual entry process. The subjective feedback from study participants indicates that the users either forgot to scan, held the phone too close to the device, did not hold the device and phone parallel, saw the button for manual entry first and used that method, or simply preferred to use the manual entry process. As designed, if the scanning is not established, the app does not proceed to the next screen, which includes a confirmatory message that indicates "injection recorded." As a result, the user opted to select the option to manually enter the injection, and this option appears at the bottom of the screen for the scanning step. Although we acknowledge some participants failed to scan the autoinjector's "smart" label, they were able to record the injections successfully using the manual entry option. In addition, we reviewed the MSDialog mobile app instructions for performing the scanning step and we did not identify any areas of concern. Thus, we find the residual risk associated with these errors acceptable and do not have any recommendations at this time.

During testing, one out of the seventeen participants required test administrator assistance while performing Task 6 (Log Out). Based on the findings of the root cause analysis EMD Serono made additional changes to the mobile app by simplifying the steps for logging out and updating the IFU accordingly. Additionally, a section was added to the frequently asked questions (FAQ) section of the mobile app to give further instruction on how to properly log out. We note that not logging out of the mobile application will not lead to patient harm. The mitigation strategy implemented by EMD Serono appears reasonable and we have no further recommendations to address this failure.

Prescribing Information (PI) and Medication Guide (MG)

We did not identify any areas of the PI or MG that require revision at this time.

Rebif Rebidose Autoinjector Instructions for Use (IFU)

On page 13 of the Rebif Rebidose Autoinjector IFU, the reader is instructed as an option to record injections "using a [redacted] (b) (4) that can [redacted] (b) (4) scan information from your autoinjector's label (see page 15)." On page 15 in the "[redacted] (b) (4)" section, the reader is informed that "If you have an Apple iPhone or google Android smartphone, you can use a [redacted] (b) (4) to record your injections." We note that this statement does not specify which app to utilize. The "MSDialog Mobile Application" should be specified in the IFU so users are clear regarding which mobile application should be utilized.

We provide recommendations in Section 5.1 for the division.

MSDialog Mobile App

During our review of the mobile app, we noticed that the app has a reminder function that also allows a patient to set a "snooze" for the reminder. However, it appears that if an injection is administered, it will not automatically cancel the reminder. We considered whether this may lead to extra doses being administered if the reminder goes off after a user has already administered their dose. We sent an IR to EMD Serono dated July 26, 2016 requesting clarification. In their response, EMD Serono indicated that if a user attempts an injection prior to when their next dose is due (too short of a time interval), a warning message will appear that the user must respond to before the app will proceed. This warning will essentially let the user know that it is too soon for another dose and they should contact their provider, then it questions whether they still intend to proceed. We find this risk mitigation measure reasonable to minimize the risk for extra dose medication errors.

EMD Serono provided two mobile phone devices loaded with the MSdialog mobile app for our review, an Android mobile device and an iPhone mobile device. In the Android mobile device provided, we set the injection time and the reminder as the IFU instructed. However, when the injection reminder fired, the app only allowed us to document an injection. There was no option to snooze as indicated in the IFU. We did not encounter this discrepancy when utilizing the mobile app with the Iphone mobile device. Thus, it appears there is a discrepancy between the IFU and the actual app that will need to be reconciled.

MSDialog Mobile App Instructions for Use (IFU)

We note that the IFU for the MSDialog Mobile App is available electronically and is a part of the mobile app. 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 there is a toll free helpline that will allow users to order printed versions of the IFU. 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 appropriate.

Additionally, during our evaluation we identified discrepancies between the mobile apps submitted on the mobile phone devices and the IFU. In particular, we note that the mobile app is supposed to allow for three mechanisms of recording the injection: (1) manual entry, (2) 2-D barcode, and (3) NFC tag. However, the IFU submitted does not include the screens seen in the mobile app that direct patients to choose the manual entry option (IFU pages 80 through 101 in submitted IFU). The IFU should be updated for consistency with the mobile app and to ensure that users are given explicit instructions on how to manually enter their injection. We note that this was tested in the HF validation study using the mobile app. No failures related to manual entry of the injection were seen during the HF validation study. These changes can be implemented without requiring further HF testing.

We also note that the use of the terminology “injection reminder” and “injection time” are used interchangeably between the electronic IFU and the actual mobile app screens. This may lead to confusion for patients as was noted by some participants in the HF validation study. This should be addressed to minimize the risk for confusion.

We provide letter-ready recommendations in Section 5.2 that should be conveyed to EMD Serono and addressed before approval of the supplement.

5 CONCLUSION & RECOMMENDATIONS

EMD Serono has submitted sufficient evidence to conclude that the user interface supports the safe and effective use of the product. Our review identified areas of the autoinjector IFU, mobile app IFU, and mobile app that require further revision to minimize the risk for medication error and provide further clarity. We recommend the changes outlined below are implemented prior to approval of this supplement. These modifications will not require additional human factors testing.

5.1 RECOMMENDATIONS FOR THE DIVISION

A. Rebif Rebidose Autoinjector Instructions for Use (IFU)

1. To promote clarity within the labeling and decrease risk of medication error with the use of Rebif Rebidose Autoinjector, we recommend you identify the MSDialog mobile app as the (b) (4) compatible with Rebif Rebidose Autoinjector. Specifically, replace the words (b) (4)" with "MSDialog mobile app" in the Rebif Rebidose Autoinjector IFU pages 13-15.

5.2 RECOMMENDATIONS FOR EMD SERONO

We recommend the changes outlined below are implemented prior to approval of this supplement. These modifications will not require additional human factors testing.

A. MSDialog Mobile App

1. In the Android mobile device sample provided, we set the injection time and the reminder as the IFU instructed. However, when the injection reminder fired, the app only allowed us to document an injection. There was no option to snooze as indicated in the IFU. Thus, it appears there is a discrepancy between the IFU and the actual app that will need to be reconciled. We did not encounter this discrepancy when utilizing the mobile app with the Iphone mobile device. Ensure this discrepancy is addressed so that the app is consistent with the electronic IFU.
2. During registration of the product, users are required to view a tutorial in the mobile app. As part of the tutorial, a warning note was added after you completed your HF validation study stating that (b) (4) (b) (4) We note that this change was not validated with further HF testing. We are concerned that this change to the tutorial may not be adequate to minimize the risk for this type of failure. We recommend that a similar warning is placed on the screen when a patient begins to record an injection so that the warning is reinforced and the patient knows before they begin recording an injection that what is entered cannot be deleted. Corresponding changes for consistency should be made to the electronic IFU.
3. After receiving an injection reminder alert, users are presented with a (b) (4) (b) (4) option. The label on the warning does not specify whether the entire injecition regimen is (b) (4) To promote clarity, we recommend the (b) (4) label be clarified to include exactly what is being (b) (4) Alternatively you can consider changing the wording for clarity (b) (4) (b) (4).

B. MSDialog Mobile App Instructions for Use (IFU)

1. We identified discrepancies between the mobile apps submitted on the mobile phone devices and the IFU. In particular, we note that the mobile app is supposed to allow for three mechanisms of recording the injection: (1) manual entry, (2) 2-D barcode, and (3) NFC tag. However, the IFU submitted does not include the screens seen in the mobile app that direct patients to choose the manual entry option (IFU pages 80 through 101 in submitted IFU). The IFU should be updated for consistency with the mobile app and to ensure that users are given explicit instructions on how to manually enter their injection.
2. We note that the use of the terminology "injection reminder" and "injection time" are used interchangeably between the electronic IFU and the actual mobile app screens. This may lead to confusion for patients as was noted in the HF validation study. The IFU should be updated to clarify that setting the injection time will also set the reminder time. On page (b) (4) of the electronic IFU that was submitted the bullet reads, "Tap the Injection (b) (4) button to schedule the time at which your injection should occur." We recommend revising that to read, "Tap the Injection time button to schedule the time at which your injection should occur. Setting the injection time will set the reminder time. (b) (4) Additionally, on page (b) (4) of the electronic IFU that was submitted the bullet reads, "The Injection (b) (4) button to change the timing of your injection during the day." We recommend revising that section to read, "Set the Injection time button to change the timing of your injection during the day. Setting the injection time will set the reminder time."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX C. HUMAN FACTORS VALIDATION STUDY PROTOCOL EXCERPTS-Study Design

Combination product description:	MSdialog Mobile Application (Companion App)
Intended users	Relapsing Multiple Sclerosis (RMS) Patients
Intended use	a tracking tool and medication reminder; Patients will add injection data and (b) (4) related to the their prescribed medication regimen and treatment.
Intended use environment	Home environment
Study objective	To ensure that the Companion App's Rebif® module and the IFU are not vulnerable to potentially harmful use that could lead to clinically significant delays in therapy or patient injury.
Method	Observation and Simulated Use; Observation of tasks performed to demonstrate successful use of the Companion app for to record injections using the device and accompanying labels, labeling and instructions for use (IFU).
Study Group	17 RMS patients with one or more self-reported neurological deficits which typically include visual, cognitive, and/or upper extremity deficits. All participants had smartphone and self-injection experience using an auto-injector, pre-filled syringe, pen-injector or other injection device. • 14 female • 3 male • age range: 35-67 years old
Training	None. All participants are self-trained with intend-to-market materials
Tasks	1. Create new account/independent exploration period 2. Record injection in real-time/responding to injection reminder 3. Record injection the day after injection 4. Interpret calendar information 5. Change injetion reminders 6. Log out 7. Find and interpret auto injector scanning instructions

APPENDIX F. BACKGROUND AND OTHER SOURCES USED FOR THIS REVIEW

BACKGROUND

The proposed MSdialog System includes the MSdialog mobile app for patient use and the MSdialog web app for both patient and health care provider use. RMS patients may use the optional MSdialog mobile App to log their injection times and injection reminders either manually or by scanning the labels 2D barcode or NFC tag. When the patient's smartphone has internet access, the recorded data synchronizes via a secure internet connection from the MSdialog mobile app to the MSdialog web app.

EMD Serono also proposes with this submission the MSdialog Web app, which is a web-based application that provide access to patient information and injection data for doctors, nurses, and patients. For RMS patient, the primary user interface of the web application is to log in, view, and edit personal information and clinical dashboards (b) (4) For Health Care Providers (HCPs) the primary user interface is to view important information related to their patients' treatment (b) (4) . In the future, (b) (4)

To better inform our review, an Information Request (IR) was sent to the sponsor on February 25, 2016 to request the sponsor re-organize the HFS results according to use error instead of by perceived severity of error and to also provide root cause analysis, subjective data, use errors associated with each task, number of participants committing the error and any proposed mitigations to the performed error. In the March 18, 2016 reply, the sponsor explained that the information for the MSdialog mobile app had no safety related use failures, and the information we requested was purposely not included in the results document.

On April 4, 2016, we sent a second IR to request subjective data and root cause analysis data for specific reported failures with the MSdialog mobile app (see Appendix F). In their April 6, 2016 response the data we requested was provided.

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LOLITA G WHITE
09/20/2016

QUYNHNHU T NGUYEN
09/20/2016

IRENE Z CHAN
09/22/2016

FINAL LABEL AND LABELING REVIEW

Date:	September 16, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products
Through:	Ralph Bernstein, PhD, Labeling Reviewer Division of Biotechnology Review and Research IV
Application:	BLA 103780/5196
Product:	Rebif Rebidose (interferon beta-1b) autoinjector
Applicant:	EMD Serono, Inc.
Submission Date:	November 27, 2015

Executive Summary:

The container labels and carton labeling for Rebif Rebidose (interferon beta-1b) autoinjector were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. The container labels and carton labeling submitted on November 27, 2015 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 103780/5196 Rebif Rebidose (interferon beta-1b) autoinjector on November 27, 2015 which is an efficacy supplement that provides for a new container label that contains a two dimensional (2D) barcode and a Near Field Communication (NFC) tag. The intended use of the 2D barcode and NFC tag is to work with a mobile application (MS dialog Mobile Application) to electronically track product use. The product quality reviewer concluded that the Applicant provided data that demonstrate that Rebif DP is not adversely affected by exposure to RFEM in studies representing real time/real world exposure. This review evaluates the revised container labels and carton labeling. Table 1 lists the product characteristics of Rebif Rebidose (interferon beta-1b).

Table 1: Proposed Characteristics of Rebif Rebidose (interferon beta-1b).

Proprietary Name:	Rebif Rebidose
Proper Name:	interferon beta-1b
Indication:	interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability
Dose:	4.4 mcg to 22 mcg subcutaneously three times per week
Route of Administration:	subcutaneous
Dosage Form:	Injection
Strength and Container-Closure:	Prefilled syringe 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, 44 mcg/0.5 mL Rebidose autoinjector 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, 44 mcg/0.5 mL
Storage and Handling:	Store refrigerated between 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. If needed, REBIF may be stored between 36°F to 77°F (2°C to 25°C) for up to 30 days and away from heat and light, but refrigeration is preferred.

Materials Reviewed:

Application 103780 - Sequence 0213 - 0213 (1172) 11/27/2015 SUPPL-5196 (Efficacy) /New/Supplement

Autoinjector Container Labels

Autoinjector Carton Labeling

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Discussion of Proposed Labeling

A. Carton Labeling

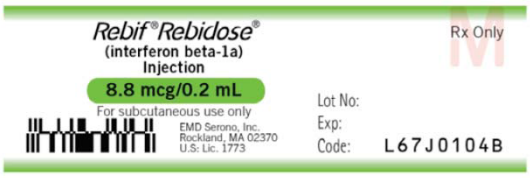
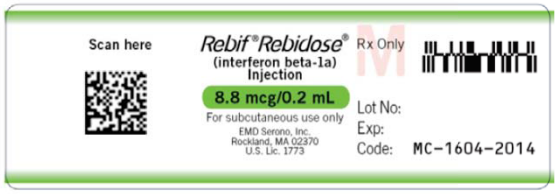
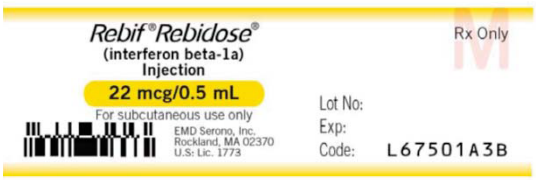
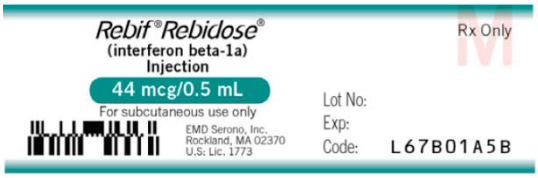
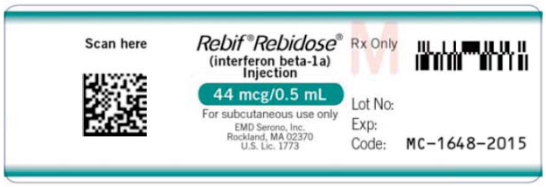
The Applicant revised the image of the autoinjector. This is acceptable.

B. Container Labels

The Applicant rearranged the information on the label to allow for inclusion of the 2D barcode and NFC tag. See below for a comparison of the currently approved container label and the proposed container label.

All the required and critical information is readable. The 2D barcode appears away from the mandatory linear barcode. This label revision is acceptable.

\\cdsesub1\evsprod\bla103780\0186\m1\us\114-labeling\114a-draft-label\rebidose-immediate-container-labels-comparison-jan-2015.pdf

Currently Approved Labels (24 mm x 65 mm)	Proposed new Data Matrix / NFC code Labels (27 mm x 81 mm)
	
	
	

Conclusions:

The container labels and carton labeling for Rebif Rebidose (interferon beta-1b) autoinjector were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. The container labels and carton labeling submitted on November 27, 2015 are acceptable.

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/s/

JIBRIL ABDUS-SAMAD
09/16/2016

CRISTINA AUSIN-MORENO
09/16/2016

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

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

Memorandum

Date: September 15, 2016

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

Tracy Peters, PharmD, Acting Associate Director for Labeling, DNP

Nahleen Lopez, PharmD, 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 103780, S-5196**
OPDP labeling comments for Rebif (interferon beta-1a), for subcutaneous injection

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This is in response to DNP's consult request dated August 24, 2016, to review the draft carton and container labeling and the following draft Instructions for Use (IFU) for the Rebif Rebidose autoinjector:

- IFU Rebif Rebidose NFC - Word - Aug2016
- IFU MSdialog Mobile App - Word - Aug2016
- IFU MSdialog Patient - Word - Aug2016
- IFU MSdialog Field Nurse - Word - Aug2016
- IFU MSdialog HCP - Word - Aug2016.

This supplement application proposes to modify the label adhered to the Rebif Rebidose to provide patients with optional electronic monitoring capability using a manual autoinjector. This proposed change is a new feature to the label by embedding the variable data (lot number, expiry date, product ID number) onto the autoinjector label with two additional formats: a 2D barcode (Data Matrix), and a Near Field Communication (NFC) tag. The NFC tag consists of a chip coupled to an antenna that is embedded on the backside of the autoinjector label.

General Comment

OPDP acknowledges DNP's September 13, 2016, Information Request in which DNP requested that the Sponsor (in pertinent part), ". . . remove (b) (4) (b) (4) and substitute claims that the applications will keep a record of injections and help keep a record for future discussions with caretakers." OPDP concurs with DNP's recommendations.

Carton and Container Labeling:

OPDP has reviewed the proposed carton and container labeling submitted to FDA on November 25, 2015, that was obtained from the DARRTS/Global Submit, and has no comments at this time.

Instructions for Use (IFU):

OPDP has conducted a high level review of the above listed IFUs obtained from DNP's SharePoint on September 7, 2016.

We note that the following IFUs do not include content or claims pertaining to the Rebif drug product, and therefore we defer to FDA's Center for Devices and Radiological Health (CDRH) for review of these materials:

- IFU MSdialog Patient - Word - Aug2016
- IFU MSdialog Field Nurse - Word - Aug2016
- IFU MSdialog HCP - Word - Aug2016.

OPDP has reviewed the proposed IFUs listed below and provides the following comments. Please note that our 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:

- IFU Rebif Rebidose NFC - Word - Aug2016
- IFU MSdialog Mobile App - Word - Aug2016

The "Getting Started Set Rebif® Settings" and "Glossary" sections of the draft IFU MSdialog Mobile Application, and the "Welcome" section of the draft IFU for Rebif Rebidose include (b) (4) however, they fail to include balancing risk information. While the IFU for Rebif Rebidose includes some information pertaining to injection site reactions, this information is not sufficient. OPDP recommends revising the IFUs to include sufficient disclosure of the most serious and most common risks associated with Rebif in depth and detail (b) (4) Alternatively, OPDP recommends deleting (b) (4) of the drug from the IFUs for consistency with the IFUs for other autoinjectors used for the treatment of relapsing MS. For example, we note that the IFU for the Plegridy and

Betaconnect autoinjectors do not include [redacted] (b) (4)

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

Thank you for the opportunity to comment.

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ALINE M MOUKHTARA
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