DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761032

BLA APPROVAL

Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL)
c/o Valeant Pharmaceuticals North America LLC
Attention: Karen M. Krstulich
Executive Director Regulatory Affairs
400 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Dear Ms. Krstulich:

Please refer to your Biologics License Application (BLA) dated and received November 16, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Siliq (brodalumab).

We also refer to our approval letter dated February 15, 2017 which contained the following errors:

- The dating period for Siliq shall be 12 months from the date of manufacture when stored at 2-8°C.
- The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4)

This replacement approval letter incorporates the corrections of the errors. The effective approval date will remain February 15, 2017, the date of the original approval letter.

We acknowledge receipt of your major amendment dated October 18, 2016, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2053 to Valeant Pharmaceuticals Luxembourg S.a.r.l. (VPL), Grand Duchy of Luxembourg, Luxembourg, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Siliq (brodalumab). Siliq is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture brodalumab drug substance at (b) (4) (b) (4). The 210 mg/1.5 mL drug product will be manufactured at (b) (4) and packaged and labeled at (b) (4) (b) (4). You may label your product with the proprietary name, Siliq, and market it in a 210 mg/1.5 mL pre-filled syringe.

DATING PERIOD

The dating period for Siliq shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4).

We have approved the stability protocols in your license application for the purpose of extending the expiration dating periods of your drug substance and drug product under 21 CFR 601.12. Data supporting extension of the expiration dating period should be submitted to the BLA Annual Report.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Siliq to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Siliq, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

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

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide and Instructions for Use). 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.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and carton and immediate container labels submitted on December 13, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015)". 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 "**Final Printed Carton and Container Labels for approved BLA 761032**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for ages < 6 years because necessary studies are impossible or highly impracticable. This is because the prevalence of psoriasis in the 0 to less than 6 years age group is low (with the highest published prevalence of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.

We are deferring submission of your pediatric studies for ages 6 to <18 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected. Based on the immunomodulatory mechanism of action for brodalumab, pediatric studies in population 6-17 years of age with moderate to severe psoriasis will likely be deferred at least until after adult studies have been completed and a determination of safety and efficacy has been made for adult psoriasis subjects.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

3164-1 Open-label study to determine PK of a single dose of brodalumab in 16 children (6 to < 18 years old) with severe plaque psoriasis.

Final Protocol Submission:	06/17
Study Completion:	01/19
Final Report Submission:	06/19

3164-2 Double-blind, active comparator-controlled, multicenter study with brodalumab to determine the safety and efficacy in adolescent subjects (12 to < 18 years old) with severe plaque psoriasis.

Final Protocol Submission:	04/19
Study Completion:	01/24
Final Report Submission:	06/24

3164-3 Open label, single arm study with brodalumab to determine safety and efficacy in children (6 to <12) with severe plaque psoriasis.

Final Protocol Submission:	04/24
Study Completion:	01/29
Final Report Submission:	06/29

Submit the protocols to your IND 104671, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of maternal, fetal and neonatal toxicity as well as an unexpected serious risk of malignancy, opportunistic infections, and neutropenia.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3164-4 Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women with a diagnosis of psoriasis exposed to brodalumab versus a non-brodalumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	12/22
Final Report Submission:	06/23

3164-5 Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women with the diagnosis of psoriasis exposed to brodalumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/17
Study Completion:	06/30
Final Report Submission:	06/31

3164-6 Conduct a prospective, observational study to assess the long-term safety of Siliq (brodalumab) compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, opportunistic infections (e.g., tuberculosis [TB], opportunistic mycoses) and neutropenia. Describe and justify the choice of appropriate comparator population(s) and

estimated background rate(s) relative to brodalumab-exposed patients; clearly define the primary comparator population for the primary objective. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a prespecified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the brodalumab-exposed and comparator(s) cohorts, clearly define the study drug initiation period, including any exclusion and inclusion criteria. Enroll patients over an initial 4 year period and follow for a minimum of 8 years from the time of enrollment.

The timetable you submitted on December 23, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission	08/17
Final Protocol Submission:	03/18
Study Completion:	11/30
Final Report Submission:	11/31

Submit the protocols to your IND 104671, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3164-7	Submit final study report for LC/UV/MS analysis using appropriate control samples to confirm the capability of this method to detect volatile compounds in the presence of brodalumab drug product.

The timetable you submitted on December 22, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/17

Submit chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Siliq (brodalumab) to ensure the benefits of the drug outweigh the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq.

Your proposed REMS must include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Siliq (brodalumab) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of observed suicidal ideation and behavior (SIB) in subjects treated with Siliq that is listed in the labeling. The elements to assure safe use (ETASU) are intended to ensure that prescribers are informed about the risk of SIB observed with Siliq therapy and the need to counsel patients about this risk. The ETASU are also intended to ensure that patients are informed about the risk of SIB observed with Siliq therapy and the need to seek medical attention should they experience manifestations of suicidal thoughts and behavior, new onset or worsening depression, anxiety, or other mood changes.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers who prescribe must be specially certified.
- Pharmacies that dispense the drug are specially certified.

- The drug is dispensed to patients with evidence or other documentation of safe-use conditions.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially certified, and the drug be dispensed to patients with documentation of safe-use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS, submitted on February 13, 2017, and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Siliq (brodalumab) into interstate commerce.

The REMS assessment plan must include, but is not limited to, the following:

1. Siliq Stakeholder data (prescribers, pharmacies, patients, and distributors) per reporting period and cumulatively:
    a. Numbers of each certified/enrolled stakeholder, status of certification, and method of certification including:
        i. Number of certified prescribers by medical degree, prescriber specialty, and method of certification (email, fax, online)
        ii. Number of certified pharmacies by pharmacy type (inpatient, outpatient chain, outpatient independent) and method of certification (email, fax, online)
        iii. Number of authorized distributors and wholesalers
        iv. Number of enrolled patients and their demographics (age, gender, race)
    b. Listing and categorization of reasons enrollment is incomplete for each stakeholder category.
2. Utilization Data, per reporting period and cumulatively**:** Number of Siliq prescriptions (new and refills) dispensed stratified by:
    a. pharmacy type
    b. method of dispensing authorization (on-line versus phone)
    c. prescriber specialty
    d. patient demographics (age, gender, race)
3. Compliance Metrics, per reporting period**:**

a. Report of annual audit findings from a representative sample of 25% of certified pharmacies or one, whichever is greater, for audits conducted during the reporting period, including:

    i. What processes and procedures the REMS and distributors/wholesalers have in place to verify, prior to dispensing Siliq, that the pharmacies are certified

    ii. Any corrective actions taken to address findings of non-compliance

    iii. The status of corrective actions,

    iv. Any resulting preventative actions taken.

b. Report of findings from an audit of 25% of the certified pharmacies or one, whichever is greater, within 90 calendar days after the pharmacy places its first order of Siliq to ensure that all processes and procedures are in place and functioning

    i. This report is to include any corrective actions taken to address findings, the status of corrective actions, and any resulting preventative actions taken

c. Number of Siliq prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences.

d. Number of Siliq prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences.

e. Number of times a Siliq prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken.

f. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences.

g. Number of prescribers, pharmacies and distributors de-certified and reasons for decertification.

h. The number of and reasons for rejected prescription authorizations.

i. Failures of Rx dispensing authorization due to calls to the REMS for authorization when the Call Center was closed or when the prescriber/patient verification portion of the website was down.

j. The numbers of the most frequently asked questions to the Call Center organized by topic.

4. REMS Program implementation (to be provided in the 12 month assessment only)

    a. Product Launch Date

    b. Date when the Siliq REMS website went live

    c. Date healthcare providers could become certified online, by email, or by fax

d. Date when the REMS Program Website & Call Center are fully operational, including the online confirmation of patient authorization functionality and the availability of REMS materials

5. Evaluation of knowledge via Knowledge, Attitude and Behavior (KAB) surveys
    a. Prescribers
        i. An evaluation of knowledge of certified prescribers of the potential risk of suicidal ideation and behavior observed with Siliq therapy.
        ii. An evaluation of prescriber practice or behavior with regards to counseling patients about the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.
        iii. An evaluation of certified prescriber knowledge of Siliq REMS requirements and processes.
    b. Patients
        i. An evaluation of knowledge of patients of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.
        ii. An evaluation of patients' recall of counseling by prescriber, pharmacist, or both, on the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.
        iii. An evaluation of patient receipt of the wallet card.
    c. Pharmacies
        i. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the potential risk of suicidal ideation and behavior observed with Siliq therapy and patients' need to seek medical attention should they experience emergence or worsening of suicidal thoughts and behavior.
        ii. An evaluation of knowledge of authorized representatives and staff pharmacists in certified pharmacies of the Siliq REMS requirements and processes.

6. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified (Section 505-1(g)(3).

We remind you that, in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS

modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761032 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,

UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761032 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 761032/ S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761032/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761032/ S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761032/ S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761032

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

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 to:

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

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, 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

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

FDA BENEFIT-RISK FRAMEWORK APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an assessment of FDA's initial phase implementation of the Benefit-Risk Framework (BRF) in human drug review. A key element of this evaluation includes interviews with applicants following FDA

approval of New Molecular Entity (NME) New Drug Applications (NDAs) and original Biologic License Applications (BLAs). The purpose of the interview is to assess the extent to which the BRF provides applicants with a clear understanding of the reasoning behind FDA's regulatory decisions for NME NDAs and original BLAs.

ERG will contact you to schedule a BRF applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final reports. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to this evaluation.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SILIQ safely and effectively. See full prescribing information for SILIQ.

SILIQ™ (brodalumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SUICIDAL IDEATION AND BEHAVIOR

See full prescribing information for complete boxed warning.

- **Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. (5.1, 6.1)**
- **Prior to prescribing, weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. (5.1)**
- **Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate. (5.1)**
- **Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes. (5.1)**
- **SILIQ is available only through a restricted program called the SILIQ REMS Program. (5.2)**

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

SILIQ is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. (1)

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

- Administer 210 mg of SILIQ by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks. (2.1)

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

- Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe. (3)

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

- Crohn's disease (4)

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

- Infections: Serious infections have occurred. Consider the risks and benefits prior to initiating SILIQ in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue SILIQ until the infection resolves. (5.3)
- Tuberculosis (TB): Evaluate patients for TB infection prior to initiating treatment with SILIQ. (5.4)
- Crohn's Disease: Crohn's disease occurred during clinical trials. Discontinue SILIQ if patient develops Crohn's disease while taking SILIQ. (5.5)
- Immunizations: Avoid using live vaccines concurrently with SILIQ. (5.5)

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

Most common adverse reactions (incidence ≥1%) were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL IDEATION AND BEHAVIOR

Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. Prior to prescribing SILIQ, weigh the potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. Patients with new or worsening suicidal ideation and behavior should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes *[see Warnings and Precautions (5.1)]*.

Because of the observed suicidal behavior in subjects treated with SILIQ, SILIQ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SILIQ REMS Program *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

SILIQ™ is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended SILIQ dose is 210 mg administered by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

If an adequate response has not been achieved after 12 to 16 weeks of treatment with SILIQ, consider discontinuing therapy. Continued treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.

2.2 Tuberculosis Assessment Prior to Initiation of SILIQ

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SILIQ *[see Warnings and Precautions (5.4)]*.

2.3 Important Administration Instructions

Administer SILIQ subcutaneously. Each prefilled syringe is for single-dose only.

Instruct patients to review the Medication Guide before use (see Medication Guide). SILIQ is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject SILIQ when deemed appropriate by a healthcare professional and after proper training in subcutaneous injection technique using the prefilled syringe.

Advise patients who are self-administering to inject the full dose and to read the Instructions for Use before administration (see Instructions for Use).

Do not inject SILIQ into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis.

2.4 Preparation of SILIQ Prefilled Syringe

- Allow SILIQ prefilled syringe to reach room temperature (approximately 30 minutes) before injecting. Do not warm in any other way. Do not remove the gray needle cap on the prefilled syringe while allowing it to reach room temperature.

- Visually inspect SILIQ for particles and discoloration prior to administration. SILIQ is a clear to slightly opalescent, colorless to slightly yellow solution. A few translucent to white, amorphous proteinaceous particles may be present. Do not use SILIQ if it is cloudy or discolored or if foreign matter is present.
- Instruct patients to use the prefilled syringe and to inject the full amount (1.5 mL), which provides 210 mg of SILIQ, according to the directions provided in the Instructions for Use *[see Instructions for Use]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe. SILIQ is a clear to slightly opalescent, colorless to slightly yellow solution and may contain a few translucent to white, amorphous particles .

4 CONTRAINDICATIONS

SILIQ is contraindicated in patients with Crohn's disease because SILIQ may cause worsening of disease *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Ideation and Behavior

Suicidal ideation and behavior, including 4 completed suicides, occurred in subjects treated with SILIQ in the psoriasis clinical trials. There were no completed suicides in the 12-week placebo-controlled portion of the trials. SILIQ users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to users without such a history *[see Adverse Reactions (6.1)]*. A causal association between treatment with SILIQ and increased risk of suicidal ideation and behavior has not been established.

Prescribers should weigh the potential risks and benefits before using SILIQ in patients with a history of depression or suicidality. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation and behavior, new onset or worsening depression, anxiety, or other mood changes. Prescribers should also re-evaluate the risks and benefits of continuing treatment with SILIQ if such events occur.

Because of the observed suicidal ideation and behavior in subjects treated with SILIQ, if an adequate response to SILIQ has not been achieved within 12 to 16 weeks, consider discontinuing therapy.

SILIQ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 SILIQ REMS Program

SILIQ is available only through a restricted program under a REMS called the SILIQ REMS Program because of the observed suicidal ideation and behavior in subjects treated with SILIQ *[see Warnings and Precautions (5.1)]*.

Notable requirements of the SILIQ REMS Program include the following:
- Prescribers must be certified with the program.
- Patients must sign a Patient-Prescriber Agreement Form.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive SILIQ.

Further information, including a list of qualified pharmacies, is available at www.SILIQREMS.com or by calling the SILIQ REMS Program Call Center at 855-511-6135.

5.3 Infections

SILIQ may increase the risk of infections. In clinical trials, subjects treated with SILIQ had a higher rate of serious infections than subjects treated with placebo (0.5% versus 0.2%) and higher rates of fungal infections (2.4% versus 0.9%). One case of cryptococcal meningitis occurred in a subject treated with SILIQ during the 12-week randomized treatment period and led to discontinuation of therapy *[see Adverse Reactions (6.1)]*.

During the course of clinical trials for plaque psoriasis, the exposure-adjusted rates for infections and serious infections were similar in the subjects treated with SILIQ and those treated with ustekinumab.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SILIQ. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy for the infection, monitor the patient closely and discontinue SILIQ therapy until the infection resolves.

5.4 Risk for Latent Tuberculosis Reactivation

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SILIQ. Do not administer SILIQ to patients with active TB infection. Initiate treatment for latent TB prior to administering SILIQ.

Consider anti-TB therapy prior to initiation of SILIQ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving SILIQ for signs and symptoms of active TB during and after treatment.

5.5 Crohn's Disease

In psoriasis trials, which excluded subjects with active Crohn's disease, Crohn's disease occurred in one subject during treatment with SILIQ and led to discontinuation of therapy. In other trials, exacerbation of Crohn's disease was observed with SILIQ use.

SILIQ is contraindicated in patients with Crohn's disease.

Discontinue SILIQ if the patient develops Crohn's disease while taking SILIQ.

5.6 Immunizations

Avoid use of live vaccines in patients treated with SILIQ. No data are available on the ability of live or inactive vaccines to elicit an immune response in patients being treated with SILIQ.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of labeling:

- Suicidal Ideation and Behavior *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.3)]*
- Crohn's Disease *[see Contraindications (4), Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The overall safety population included 4558 subjects (3066 SILIQ, 613 ustekinumab, 879 placebo) in controlled clinical trials and open-label extension studies. The majority of subjects were male (69%), white (91%), and aged 40-64 years old

(58%). One-third of subjects reported previous biologic use prior to enrollment. Across the clinical development program, 4464 subjects received at least one dose of SILIQ; 3755 subjects were exposed to SILIQ for at least 1 year.

Weeks 0 to 12:
Data from one multicenter, randomized, placebo-controlled trial (Trial 1), two multicenter, randomized, placebo- and active-controlled trials (Trials 2 and 3), and one dose-finding trial (Trial 4) in plaque psoriasis were pooled to evaluate the safety of SILIQ (210 mg weekly at Weeks 0, 1, and 2, followed by treatments every 2 weeks [Q2W]) compared to placebo for up to 12 weeks after treatment initiation.

During the 12-week, randomized treatment period, about 1% of the subjects in the treatment groups (SILIQ, ustekinumab and placebo) discontinued treatment because of adverse events. Adverse events leading to discontinuation of SILIQ included neutropenia, arthralgia, and urticaria. The proportion of subjects who developed serious adverse events was similar among the SILIQ, ustekinumab, and placebo groups.

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the SILIQ 210 mg Q2W group than in the placebo group during the 12-week randomized treatment period of the pooled trials.

Table 1: Adverse Reactions Occurring in ≥ 1% of Subjects in the SILIQ Group and More Frequently than in the Placebo Group in Plaque Psoriasis Trials through Week 12

Adverse Reactions	Placebo (N=879) n (%)	SILIQ 210 mg every 2 weeks[a] (N=1496) n (%)	Ustekinumab (N=613)[b] n (%)
Arthralgia	29 (3.3)	71 (4.7)	15 (2.4)
Headache	31 (3.5)	64 (4.3)	23 (3.8)
Fatigue	10 (1.1)	39 (2.6)	16 (2.6)
Diarrhea	10 (1.1)	33 (2.2)	5 (0.8)
Oropharyngeal pain	10 (1.1)	31 (2.1)	8 (1.3)
Nausea	10 (1.1)	28 (1.9)	6 (1.0)
Myalgia	3 (0.3)	26 (1.7)	4 (0.7)
Injection site reactions (pain, erythema, bruising, hemorrhage, pruritus)	11 (1.3)	23 (1.5)	12 (2.0)
Influenza	4 (0.5)	19 (1.3)	7 (1.1)
Neutropenia	4 (0.5)	15 (1.0)	5 (0.8)
Tinea infections (tinea pedis, versicolor, cruris)	2 (0.2)	15 (1.0)	3 (0.5)

[a] subjects receiving 210 mg of SILIQ at Weeks 0, 1, and 2, followed by treatment every two weeks during the 12-week period
[b] Trials 2 and 3 included the active comparator, ustekinumab.

Adverse reactions that occurred in less than 1% of subjects in the SILIQ group through Week 12 were conjunctivitis and candida infections (including oral [0.2%], genital [0.1%], and esophageal [0.1%] versus none in the placebo group).

Week 0 to End of Trial:
Through Week 52, exposure-adjusted rates of serious adverse events were similar between subjects treated with SILIQ and those treated with ustekinumab. Through the end of the trial, the exposure-adjusted rates of treatment-emergent serious adverse events were similar to those seen in the 52-week period in the subjects treated with SILIQ.

Specific Adverse Reactions:
Suicidal Ideation and Behavior

During the 12-week randomized treatment period in the pooled trials, one subject in the SILIQ group attempted suicide and none in the placebo or ustekinumab groups. From initiation through Week 52 of the trials, suicidal ideation or behavior occurred in 7 of 4019 subjects (0.2 per 100 subject-years) treated with SILIQ and in 2 of 613 subjects (0.4 per 100 subject-years) treated with ustekinumab.

During the course of the clinical trials for plaque psoriasis, suicidal ideation or behavior occurred in 34 of 4464 subjects treated with SILIQ (0.37 per 100 subject-years). Eight of the 10 subjects who attempted or completed suicide had a history of depression and/or suicidal ideation or behavior *[see Warnings and Precautions (5.1, 5.2)]*.

Infections
During the 12-week randomized treatment period, infections occurred in 25.4% of the SILIQ group compared to 23.4% of the placebo group. The majority of infections consisted of nasopharyngitis, upper respiratory tract infection, pharyngitis, urinary tract infections, bronchitis, and influenza, and did not necessitate treatment discontinuation. The SILIQ group had a higher rate of fungal infections compared to the placebo group (1.8% vs 0.9%). The fungal infections were primarily non-serious skin and mucosal candida infections *[see Warnings and Precautions (5.3)]*.

Neutropenia
During the 12-week randomized treatment period, neutropenia occurred in 0.7% of subjects in the SILIQ group. Most adverse reactions of neutropenia were transient. In subjects with normal absolute neutrophil count (ANC) at baseline, a reduction in ANC occurred in 6.8% of subjects in the SILIQ group, compared to 3.3% in the ustekinumab group, and 3.6% in the placebo group. Neutropenia ≥ Grade 3 (< 1000/mm^3) occurred in 0.5% of subjects in the SILIQ group compared to 0.2% of subjects in the ustekinumab group and none in the placebo group. From Week 0 to end of trial, the exposure-adjusted rate of treatment-emergent neutropenia was 0.4 per 100 subject-years (0.1 per 100 subject-years were ≥ Grade 3). No serious infections were associated with cases of neutropenia.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity with SILIQ. Approximately 3% of subjects treated with SILIQ developed antibodies to brodalumab through the 52-week treatment period. Of the subjects who developed antibodies to brodalumab, none had antibodies that were classified as neutralizing. However, the assay to test for neutralizing antibodies had limitations detecting neutralizing antibodies in the presence of brodalumab; therefore, the incidence of neutralizing antibody development could be underestimated.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SILIQ with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Live Vaccinations

Avoid use of live vaccines in patients treated with SILIQ *[see Warnings and Precautions (5.6)]*.

7.2 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Treatment with SILIQ may modulate serum levels of some cytokines.

Therefore, upon initiation or discontinuation of SILIQ in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug

concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data on SILIQ use in pregnant women to inform a drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, SILIQ may be transmitted from the mother to the developing fetus. In a combined embryofetal development and pre- and post-natal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of brodalumab during organogenesis through parturition at doses up to 26 times the maximum recommended human dose (MRHD)*[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

A combined embryofetal development and pre- and post-natal development study was conducted in cynomolgus monkeys administered brodalumab. No brodalumab-related effects on embryofetal toxicity or malformations, or on morphological, functional or immunological development were observed in infants from pregnant monkeys administered weekly subcutaneous doses of brodalumab up to 26 times the MRHD from the beginning of organogenesis to parturition (on a mg/kg basis of 90 mg/kg/week).

8.2 Lactation

Risk Summary

There are no data on the presence of brodalumab in human milk, the effects on the breastfed infant, or the effects on milk production. Brodalumab was detected in the milk of lactating cynomolgus monkeys. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SILIQ and any potential adverse effects on the breastfed infant from SILIQ or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SILIQ have not been evaluated in pediatric patients.

8.5 Geriatric Use

Of the 3066 plaque psoriasis subjects initially randomized to SILIQ in clinical trials, 192 (6%) were ≥ 65 years old and no subjects were ≥ 75 years old. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 years and older was not sufficient to determine whether they responded differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Brodalumab is a human monoclonal IgG2κ antibody directed against human interleukin-17 receptor A (IL-17RA). It is expressed in a Chinese Hamster Ovary (CHO) cell line. Brodalumab is comprised of 1312 amino acids and has an estimated molecular mass of 144,000 Daltons.

SILIQ (brodalumab) Injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, delivered via subcutaneous injection. A few translucent to white, amorphous particles may be present. SILIQ is supplied in a single-dose 2.25 mL syringe made from type 1 glass with stainless steel 27G x ½" needle. Each SILIQ

single-dose prefilled syringe delivers 1.5 mL of solution containing 210 mg of brodalumab formulated in glutamate (6.5 mg), polysorbate 20 (0.15 mg), proline (36 mg), and Water for Injection, USP at pH 4.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines.

12.2 Pharmacodynamics

Elevated levels of IL-17A, IL-17C and IL-17F are found in psoriatic plaques. Serum IL-17A levels, measured at Weeks 12, 24, and 48 of SILIQ 210 mg every 2 weeks of treatment, were higher than the baseline levels in subjects with moderate to severe plaque psoriasis. The relationship between the pharmacodynamic activity and the mechanism(s) by which brodalumab exerts its clinical effects is unknown.

12.3 Pharmacokinetics

Absorption

Following a single subcutaneous dose of 210 mg in subjects with plaque psoriasis, brodalumab reached peak mean (±SD) serum concentration (C_{max}) of 13.4±7.3 mcg/mL by approximately 3 days post dose. The mean (±SD) area-under-the-concentration-time curve (AUC) of brodalumab was 111±64 mcg•day/mL.

Following multiple subcutaneous doses of 210 mg every 2 weeks, steady-state was achieved by Week 4. The mean (±SD) C_{max} was 20.6±14.6 mcg/mL and the mean (±SD) AUC over the two week dosing interval was 227±167 mcg•day/mL.

Following subcutaneous administration, brodalumab bioavailability was approximately 55%.

Distribution

Following a single subcutaneous administration of brodalumab 210 mg in subjects with plaque psoriasis, the mean (±SD) apparent volume of distribution (Vz/F) of brodalumab was 8.9±9.4 L.

Elimination

The metabolic pathway of brodalumab has not been characterized. As a human monoclonal IgG2 antibody, brodalumab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Following a single subcutaneous administration of brodalumab 210 mg in subjects with plaque psoriasis, the mean (±SD) apparent total clearance (CL/F) was 3.0±3.5 L/day. The clearance of brodalumab increased with decreasing doses due to nonlinear elimination.

Dose Linearity

Brodalumab exhibited non-linear pharmacokinetics with exposures that increased greater than dose-proportionally over a dose range from 140 mg (approximately 0.67 times the recommended dose) to 350 mg (approximately 1.67 times the recommended dose) following subcutaneous administrations in subjects with plaque psoriasis.

Weight

Brodalumab trough concentrations were lower in subjects with higher body weight.

Specific Populations

Hepatic or Renal Impairment

No trials were conducted to assess the effect of hepatic or renal impairment on the pharmacokinetics of brodalumab.

Age: Geriatric Population

Population pharmacokinetic analysis indicated that age did not significantly influence the clearance of brodalumab in subjects with plaque psoriasis. Subjects who were 65 years or older had a similar brodalumab clearance as compared to subjects less than 65 years old.

Drug Interaction Studies

In subjects with plaque psoriasis, one week following a single subcutaneous administration of 210 mg brodalumab, the exposure of midazolam (CYP3A4 substrate) was increased by 24% *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of SILIQ. The published literature is mixed on the potential effects on malignancy risk due to the inhibition of the IL-17RA, the pharmacological action of SILIQ. Some published literature suggests that IL-17A directly promotes cancer cell invasion, which suggests a potential beneficial effect of SILIQ. However, other reports indicate IL-17A promotes T-cell mediated tumor rejection, which suggests a potential adverse effect by SILIQ. However, inhibition of the IL-17RA with SILIQ has not been studied in these models. Therefore, the relevance of experimental findings in these models for malignancy risk in humans is unknown.

In cynomolgus monkeys, there were no effects on fertility parameters such as changes in reproductive organs or sperm analysis following subcutaneous administration of brodalumab at dose levels up to 90 mg/kg/week for six months (26 times the MRHD on a mg/kg basis). The monkeys were not mated in this study to evaluate effects on fertility.

14 CLINICAL STUDIES

Three multicenter, randomized, double-blind, controlled trials (Trials 1, 2, and 3) enrolled a total of 4373 subjects 18 years of age and older with at least a 6-month history of moderate to severe plaque psoriasis, defined as having a minimum affected body surface area (BSA) of 10%, a Psoriasis Area and Severity Index (PASI) score ≥ 12, a static Physician's Global Assessment (sPGA) score ≥3 in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 5, and who were candidates for systemic therapy or phototherapy. In all three trials, subjects were randomized to subcutaneous treatment with placebo or SILIQ 210 mg at Weeks 0, 1, and 2, followed by treatments every 2 weeks [Q2W] through Week 12. In the two active comparator trials (Trials 2 and 3), subjects randomized to ustekinumab received a 45 mg dose if their weight was less than or equal to 100 kg and a 90 mg dose if their weight was greater than 100 kg at Weeks 0, 4, and 16, followed by the same dose every 12 weeks.

All three trials assessed the change from baseline to Week 12 compared to placebo in the two co-primary endpoints: 1) PASI 75, the proportion of subjects who achieved at least a 75% reduction in the PASI composite score that takes into consideration both the percentage of body surface area affected and the nature and severity of psoriatic changes (induration, erythema, and scaling) within the affected region, and 2) the proportion of subjects with an sPGA of 0 (clear) or 1 (almost clear), and at least a 2-point improvement from baseline. In Trials 2 and 3, comparisons were also made to ustekinumab for the primary endpoint of the proportion of subjects who achieved a reduction in PASI score of 100% (PASI 100) from baseline at Week 12.

Other evaluated outcomes included the proportion of subjects who achieved an sPGA of 0 (clear) at Week 12, and the proportion of subjects who achieved a Psoriasis Symptom Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item (itch, redness, scaling, burning, stinging, cracking, flaking, and pain) at Week 12. Baseline demographics and disease characteristics were generally consistent across all treatment groups in all three trials. Subjects were predominantly men (69%) and white (91%), with a mean age of 45 years. The mean baseline body weight was 90.5 kg and 28% of subjects had body weight greater than 100 kg. The baseline PASI score ranged from 9.4 to 72 (median: 17.4) and the baseline affected BSA ranged from 10 to 97% (median: 21%). Baseline sPGA scores ranged from "3 (moderate)" (58%) to "5 (very severe)" (5%).

Approximately 21% of subjects had a history of psoriatic arthritis. Approximately 30% of subjects had previously received a biologic therapy and 12% of subjects had failed previous biologic therapy.

Clinical Response at Week 12

The results of Trials 1, 2, and 3 are presented in Table 2.

Table 2: Efficacy Results at Week 12 in Adults with Plaque Psoriasis in Trials 1, 2, and 3 (NRI[a])

Endpoint	Trial 1		Trial 2			Trial 3		
	SILIQ 210 mg Q2W (N=222) n (%)	Placebo (N=220) n (%)	SILIQ 210 mg Q2W (N=612) n (%)	Ustekinumab (N=300) n (%)	Placebo (N=309) n (%)	SILIQ 210 mg Q2W (N=624) n (%)	Ustekinumab (N=313) n (%)	Placebo (N=315) n (%)
PASI 75[b] response	185 (83)	6 (3)	528 (86)	210 (70)	25 (8)	531 (85)	217 (69)	19 (6)
PASI 100 response	93 (42)	1 (<1)	272 (44)[b]	65 (22)	2 (1)	229 (37)[b]	58 (19)	1 (<1)
sPGA success clear (0) or almost clear (1)[b]	168 (76)	3 (1)	481 (79)	183 (61)	12 (4)	497 (80)	179 (57)	13 (4)
sPGA of clear (0)	93 (42)	1 (<1)	274 (45)	65 (21)	2 (1)	229 (37)	58 (19)	1 (<1)

[a]NRI = non-responder imputation

[b]Co-primary endpoints

Examination of age, gender, race, use of prior systemic or phototherapy, and use of prior biologics did not identify differences in response to SILIQ among these subgroups.

At Week 12, compared to subjects in the placebo group, a greater proportion of subjects in SILIQ 210 mg Q2W group achieved a Psoriasis Symptom Inventory (PSI) score of 0 (not at all) or 1 (mild) on every item (itch, redness, scaling, burning, stinging, cracking, flaking, pain).

Maintenance of Effect

In Trial 1, subjects randomized to receive SILIQ and who were responders at Week 12 (i.e., sPGA of 0 or 1) were re-randomized to receive either placebo or SILIQ. Among responders at Week 12, 83% (69/83) of subjects re-randomized to continued treatment with SILIQ 210 mg Q2W maintained this response (sPGA of 0 or 1) at Week 52 compared to none (0/84) who were re-randomized to placebo and withdrawn from SILIQ. In addition, 87% (72/83) of subjects re-randomized to continued treatment with SILIQ 210 mg Q2W achieved PASI 75 response at Week 52 compared to none (0/84) who were re-randomized to placebo and withdrawn from SILIQ.

Trials 2 and 3 included a re-randomized phase during which subjects originally randomized to receive SILIQ during the first 12 weeks were re-randomized to one of four SILIQ regimens at the Week 12 visit and placebo subjects were crossed

over to receive SILIQ 210 mg Q2W. Subjects receiving ustekinumab continued the same treatment until crossed over at Week 52 to SILIQ 210 mg Q2W. For sPGA 0 or 1 responders at Week 12, the percentage of subjects who maintained this response at Week 52 was 79% for subjects treated with SILIQ 210 mg Q2W. For PASI 100 responders at Week 12, 72% of the subjects who continued on SILIQ 210 mg Q2W maintained the response at Week 52.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

SILIQ (brodalumab) Injection is available in a single-dose prefilled syringe containing a sterile, preservative-free clear to slightly opalescent, colorless to slightly yellow solution that may contain a few translucent to white, amorphous particles.

- NDC 0187-0004-02: Carton of two 210 mg/1.5 mL single-dose prefilled syringes

16.2 Storage and Handling

- Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light and physical damage during storage.
- When necessary, prefilled syringes can be stored at room temperature up to a maximum of 77°F (25°C) in the original carton for a maximum single period of 14 days with protection from light and sources of heat. Once the prefilled syringe has reached room temperature, do not place back into the refrigerator. Discard after 14 days at room temperature.
- Do not freeze.
- Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)* before the patient starts using SILIQ, and each time the prescription is renewed, as there may be new information they need to know.

Suicidal Thoughts and Behavior

Instruct patients and their caregivers to monitor for the emergence of suicidal thoughts and behavior and promptly seek medical attention if the patient experiences suicidal thoughts, new or worsening depression, anxiety, or other mood changes *[see Warnings and Precautions (5.1)]*.

Instruct patients to carry the wallet card provided and to call the National Suicide Prevention Lifeline at 1-800-273-8255 if they experience suicidal thoughts.

SILIQ REMS Program

Because of the observed suicidal thoughts and behavior in subjects treated with SILIQ, SILIQ is available only through a restricted program called the SILIQ REMS Program *[see Warnings and Precautions (5.2)]*. Inform the patient of the following:

- Patients must enroll in the program *[see Warnings and Precautions (5.1, 5.2)]*.
- Patients will be given a SILIQ Patient Wallet Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation. Advise the patient to show the SILIQ Patient Wallet Card to other treating healthcare providers.

SILIQ is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Infections

Inform patients that SILIQ may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to their healthcare providers and to contact their healthcare providers if they develop any signs or symptoms of infection *[see Warnings and Precautions (5.3)]*.

Crohn's Disease

Instruct patients to seek medical advice if they develop signs and symptoms of Crohn's disease *[see Warnings and Precautions (5.5)]*.

Instructions for Injection

Instruct the patient to perform the first self-injection under the guidance and supervision of a qualified healthcare professional for proper training in subcutaneous injection technique.

Instruct patients who are self-administering to inject the full dose of SILIQ *[see Dosage and Administration (2.1) and Instructions for Use]*.

Instruct patients or caregivers in the technique of proper syringe and needle disposal *[see Instructions for Use]*.

Manufactured for:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Valeant Pharmaceuticals Luxembourg S.à.r.l.
Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number 2053

U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673

Issued: February/2017

1

Medication Guide
SILIQ™ (SIL-EEK)
(brodalumab)
injection, for subcutaneous use

What is the most important information I should know about SILIQ?

SILIQ may cause serious side effects, including:

- **Suicidal thoughts or behavior have happened in** some people treated with SILIQ. Some people have ended their own lives. Your risk of suicidal thoughts and behavior may be increased if you have a history of suicidal thoughts or depression. It is not known if SILIQ causes suicidal thoughts or behavior. Get medical help right away if you or your caregiver notice any of the following symptoms:
  - o new or worsening depression or anxiety
  - o thoughts of suicide, dying, or hurting yourself
  - o changes in behavior or mood
  - o acting on dangerous impulses
  - o attempt to commit suicide

Your healthcare provider will give you a SILIQ Patient Wallet Card about symptoms you should get medical help for right away. Carry the card with you at all times during treatment with SILIQ and show it to all of your healthcare providers.

- **Serious infections.** SILIQ may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider will check you for tuberculosis (TB) before starting treatment with SILIQ and may treat you for TB before you begin treatment with SILIQ if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of infection and TB during and after treatment with SILIQ.
  Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including:
  - o fever, sweats, or chills
  - o muscle aches
  - o cough
  - o shortness of breath
  - o sore throat or difficulty swallowing
  - o warm, red, or painful skin or sores on your body
  - o diarrhea or stomach pain
  - o burning when you urinate or urinate more often than normal

See **"What are the possible side effects of SILIQ?"** for more information about side effects.

What is SILIQ?

SILIQ is a prescription medicine used to treat adults with moderate to severe plaque psoriasis:

- who may benefit from taking injections or pills (systemic therapy) or phototherapy (ultraviolet light treatment)**, and**
- who have not responded or lost response to other systemic therapy

It is not known if SILIQ is safe and effective in children.

Do not use SILIQ if you have Crohn's disease.

Before you use SILIQ, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of mental problems, including suicidal thoughts, depression, anxiety, or mood problems.
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- have recently received or are scheduled to receive an immunization (vaccine). You should avoid receiving live vaccines during treatment with SILIQ.
- are pregnant or plan to become pregnant. It is not known if SILIQ can harm your unborn baby. If you are pregnant or plan on becoming pregnant, consult with your healthcare provider.
- are breastfeeding or plan to breastfeed. It is not known if SILIQ passes into your breast milk.

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

How should I use SILIQ?

- **See the detailed "Instructions for Use" that comes with SILIQ for information on how to inject a dose of SILIQ and how to properly store and throw away (dispose of) used SILIQ prefilled syringes.**
- Use SILIQ exactly as your healthcare provider tells you to use it.
- Your healthcare provider may stop SILIQ if your plaque psoriasis does not improve within 12 to 16 weeks of treatment.

What are the possible side effects of SILIQ?

SILIQ may cause serious side effects. See "What is the most important information I should know about SILIQ?"

- **Crohn's disease.** Tell your healthcare provider if you develop diarrhea, painful diarrhea, bloody stools, stomach pain or cramping, sudden or uncontrollable bowel movements, loss of appetite, constipation, weight loss, fever, or tiredness.

The most common side effects of SILIQ include: joint pain, headache, tiredness, diarrhea, mouth or throat pain, nausea, muscle pain, injection site reactions, flu (influenza), low white blood count (neutropenia), and fungal infections of the skin.

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

General information about safe and effective use of SILIQ

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SILIQ for a condition for which it was not prescribed. Do not give SILIQ to other people even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about SILIQ that is written for health professionals.

Manufactured for: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA
Manufactured by: Valeant Pharmaceuticals Luxembourg S.à.r.l., Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number 2053, Part number *XXXX*
For more information, go to www.SILIQ.com or call Valeant Pharmaceuticals at 1-800-321-4576.
U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: February/2017
Reference ID: 4067005

Instructions for Use

SILIQ is supplied as a single-dose prefilled syringe. Each prefilled syringe contains one 210 mg dose of SILIQ. **Each SILIQ prefilled syringe can only be used one time.**

Your healthcare provider has prescribed SILIQ and will tell you how often it should be injected. If your healthcare provider decides that you or a caregiver may be able to give your injections of SILIQ at home, you should receive training on the right way to prepare and inject SILIQ. Do not try to inject yourself until you have been shown the right way to give the injections by your healthcare provider.

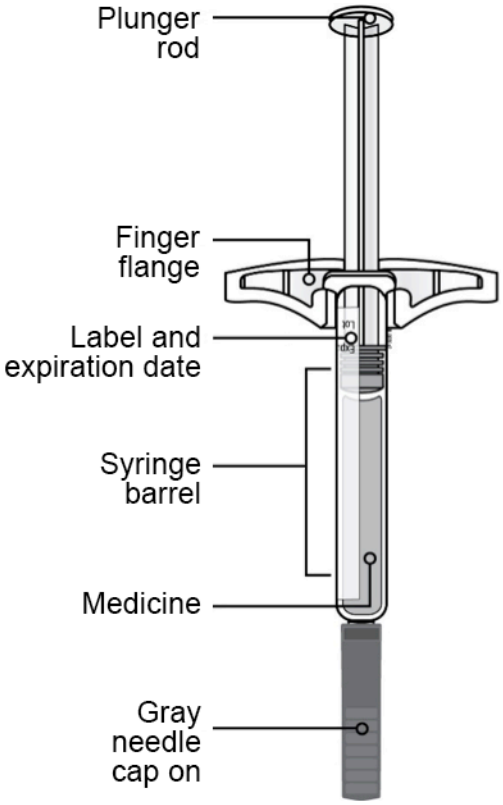
Read all of the instructions before using the SILIQ prefilled syringe. Call your healthcare provider if you or your caregiver have any questions about the right way to inject SILIQ.

Instructions for Use
SILIQ™ (SIL-EEK)
(brodalumab)
injection, for subcutaneous use

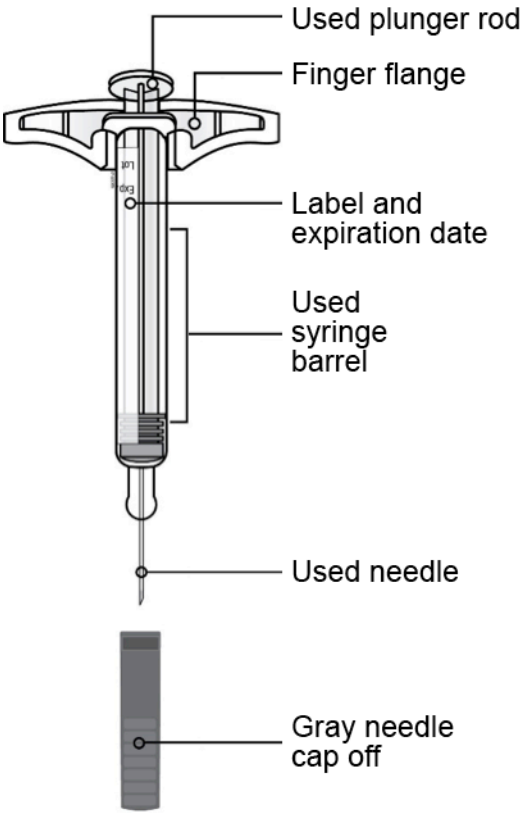
Single-Dose Prefilled Syringe

Guide to parts

Before use



After use



Important: Needle is inside the gray needle cap.

Important

Storing your SILIQ prefilled syringe

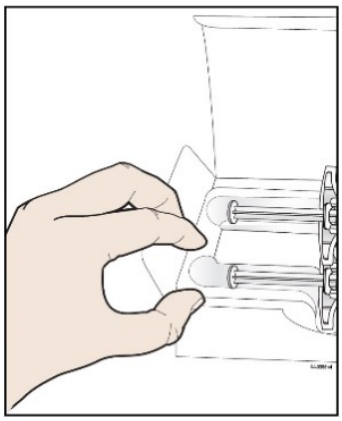
- Store SILIQ prefilled syringe in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C).
- If needed, SILIQ prefilled syringe may be stored at room temperature up to 77°F (25°C) for up to 14 days. **Do not** place SILIQ prefilled syringe stored at room temperature back into the refrigerator.
- Throw away SILIQ prefilled syringe that has been stored at room temperature after 14 days.
- Protect SILIQ prefilled syringe from heat.
- **Do not** freeze.
- Keep SILIQ prefilled syringe in the original carton to protect from light and physical damage.
- Keep SILIQ prefilled syringe and all medicines out of reach of children.

Using your SILIQ prefilled syringe

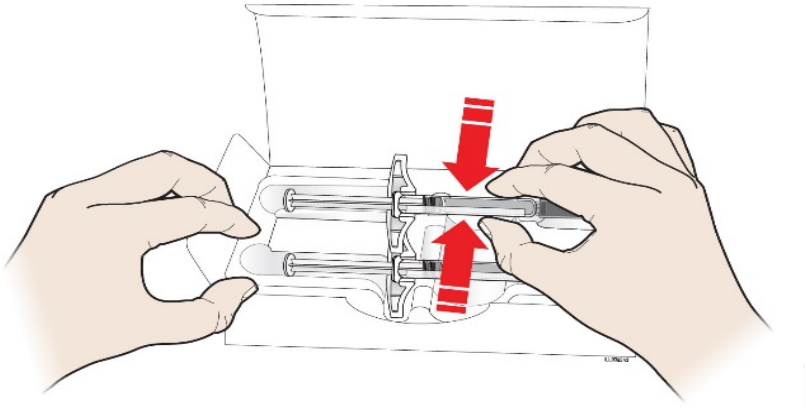
- It is important that you do not try to give the injection unless you or your caregiver has received training from your healthcare provider.
- **Do not** use a SILIQ prefilled syringe after the expiration date on the label.
- **Do not** shake the SILIQ prefilled syringe.
- **Do not** remove the gray needle cap from the SILIQ prefilled syringe until you are ready to inject.
- **Do not** use a SILIQ prefilled syringe if it has been dropped on a hard surface. Part of the SILIQ prefilled syringe may be broken even if you cannot see the break. Use a new SILIQ prefilled syringe, and call 1-800-321-4576.

Step 1: Prepare

A Remove one SILIQ prefilled syringe from the package.
Grab the syringe by the barrel to remove the prefilled syringe from the tray.



Place your finger or thumb on the edge of the tray to hold it while you remove the prefilled syringe.



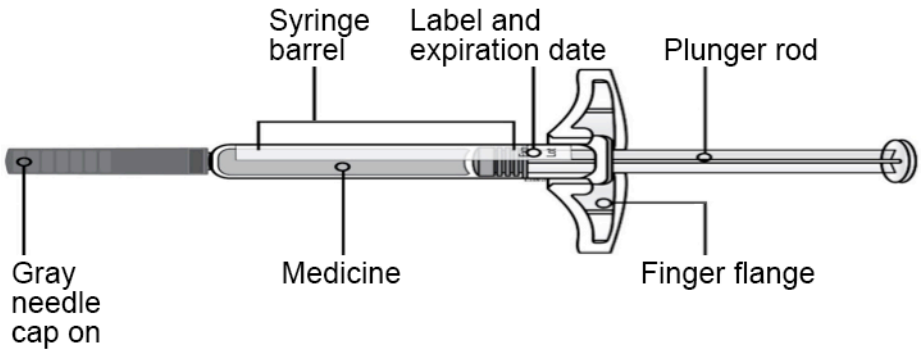
Put the original package with any unused prefilled syringes back in the refrigerator.

For safety reasons:
- **Do not** grab the plunger rod.
- **Do not** grab the gray needle cap.
- **Do not** remove the gray needle cap until you are ready to inject.

Wait about 30 minutes to let the prefilled syringe warm to room temperature before you use it.
- **Do not** put the prefilled syringe back in the refrigerator after it has reached room temperature.
- **Do not** try to warm the prefilled syringe by using a heat source such as hot water or microwave.
- **Do not** leave the prefilled syringe in direct sunlight.
- **Do not** shake the prefilled syringe.

Important: Always hold the prefilled syringe by the syringe barrel.

B Inspect the SILIQ prefilled syringe.



Make sure the medicine in the prefilled syringe is clear and colorless to slightly yellow.

- **Do not** use the syringe if:
  - The medicine is cloudy or discolored or contains flakes or particles.
  - Any part appears cracked or broken.
  - The gray needle cap is missing or not securely attached.
  - The expiration date printed on the label has passed.

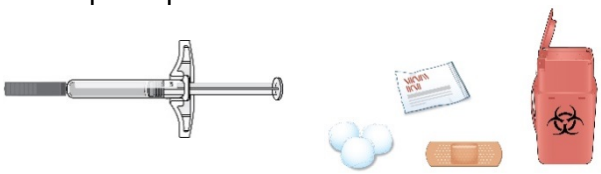
In all cases, use a new prefilled syringe, and call 1-800-321-4576.

C Gather all materials needed for your injection.

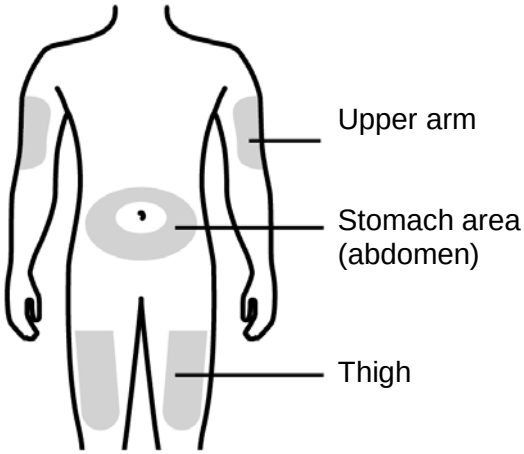
Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- Prefilled syringe
- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container



D Prepare and clean your injection site.



You can use:

- Your thigh
- Stomach area (abdomen), except for a **2**-inch area right around your navel (belly button)
- Outer area of upper arm (only if someone else is giving you the injection)

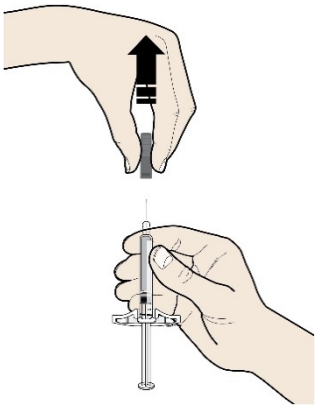
Clean your injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection. If you want to use the same injection site, make sure it is not the same spot on the injection site that you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

- Avoid injecting directly into raised, thick, red, or scaly skin patch or lesion.

Step 2: Get ready

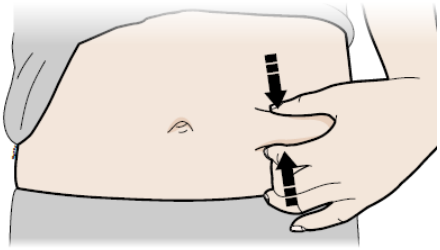
E Pull the gray needle cap straight off and away from your body when you are ready to inject.



It is normal to see a drop of liquid at the end of the needle.
- **Do not** twist or bend the gray needle cap.
- **Do not** put the gray needle cap back onto the prefilled syringe.
- **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.

Important: Throw the needle cap into the sharps disposal container provided.

F Pinch your injection site to create a firm surface.

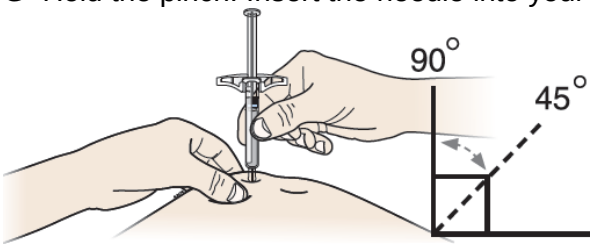


Pinch skin firmly between your thumb and fingers, creating an area about **2** inches wide.

Important: Keep skin pinched while injecting.

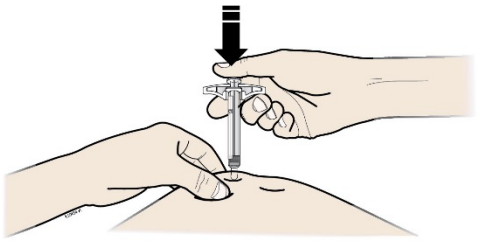
Step 3: Inject

G Hold the pinch. Insert the needle into your skin at 45 to 90 degrees.

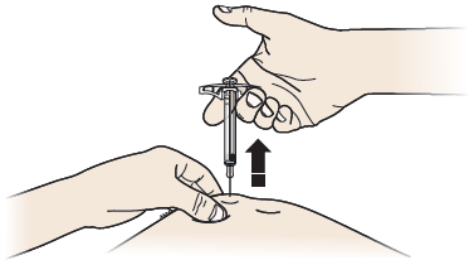


Do not place your finger on the plunger rod while inserting the needle.

H Using slow and constant pressure, push the plunger rod all the way down until it reaches the bottom.



I When done, release your thumb, and gently lift the syringe and pull the needle out of your skin.



J Inspect the syringe. If there is still medicine in the syringe barrel, this means you have not received a full dose. Call your healthcare provider right away.

Step 4: Finish

K Discard (throw away) the used syringe.

- Put the used SILIQ syringe in an FDA-cleared sharps disposal container right away after use. **Do not** throw away (dispose of) the syringe in your household trash.
- If you do not have an 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.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** reuse the syringe.
- **Do not** recycle the syringe or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the reach of children.

L Examine the injection site.
If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

Manufactured for:
Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

Manufactured by:
Valeant Pharmaceuticals Luxembourg S.à.r.l.
Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number 2053

For more information, go to www.SILIQ.com or call Valeant Pharmaceuticals at 1-800-321-4576.

U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673

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

Part number *XXXX*
Issued: February/2017


No Varnish
No Print Viewing Window
1015165
LOT
EXP
NDC 0187 0004 00
Rx only
Single-Dose Prefilled Syringe
SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL
For Subcutaneous Use Only
Manufactured by: Valeant Pharmaceuticals Luxembourg S.à r.l.
©Valeant Pharmaceuticals North America LLC
(01)00301870004007
9537500
No Varnish Area

Barcode
Human Readable

Rx only

Carton contents:
- 1 Medication Guide
- 1 Instructions for Use
- 1 Package Insert
- 2 Prefilled Syringes

See package insert for dosing information and Instructions for Use.

210 mg/1.5 mL

For Subcutaneous Use Only

ATTENTION: Dispense with enclosed medication guide.
Sterile Solution - No Preservative
KEEP OUT OF REACH OF CHILDREN.

SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL

NDC 0187-0004-02

Contains 2 Single-Dose Prefilled Syringes

Glue Flap

Manufactured for: Valeant Pharmaceuticals North America, LLC
Bridgewater, NJ 08807
Manufactured by: Valeant Pharmaceuticals Luxembourg S.à.r.l.
Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number xxxx
No U.S. standard of potency.
U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673
Siliq is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.

9537400

3 01870 00402 1

Contains 2 Single-Dose Prefilled Syringes **Rx only**

SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL

For Subcutaneous Use Only

210 mg/1.5 mL

See package insert for dosing information and Instructions for Use.

Carton contents:
- 2 Prefilled Syringes
- 1 Package Insert
- 1 Instructions for Use
- 1 Medication Guide

VALEANT

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.
When necessary, SILIQ can be stored at room temperature up to a maximum of 77°F (25°C) in original carton for a maximum single period of 14 days with protection from light and sources of heat. Once SILIQ reaches room temperature, do not place back in refrigerator. Discard after 14 days at room temperature.
Date removed from refrigerator __/__/__

NDC 0187-0004-02 **Contains 2 Single-Dose Prefilled Syringes**

SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL

For Subcutaneous Use Only **Rx only**

Each single-dose prefilled syringe delivers 1.5 mL of solution containing brodalumab 210 mg, glutamate (6.5 mg), polysorbate 20 (0.15 mg), proline (36 mg), and Water for Injection.
ATTENTION: Dispense with enclosed medication guide.

VALEANT

1015164

LOT
EXP

Serialization, Lot & Exp Area

Glue Flap

Manufactured for: Valeant Pharmaceuticals North America, LLC
Bridgewater, NJ 08807
Manufactured by: Valeant Pharmaceuticals Luxembourg S.à.r.l.
Grand Duchy of Luxembourg, L-1931, Luxembourg
U.S. License Number xxxx
No U.S. standard of potency.
U.S. Patents 7,939,070; 7,786,284; 7,833,527; 7,767,206; 8,790,648; 8,545,842; 8,435,518; 9,073,999; 9,096,673
Siliq is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.
©Valeant Pharmaceuticals North America LLC
9537300

3 01870 00401 4

Contains 1 Single-Dose Prefilled Syringe **Rx only**

SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL
For Subcutaneous Use Only

210 mg/1.5 mL

SAMPLE - NOT FOR RESALE

See package insert for dosing information and Instructions for Use.

Carton contents:
- 1 Prefilled Syringe
- 1 Package Insert
- 1 Instructions for Use
- 1 Medication Guide

VALEANT

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.
When necessary, SILIQ can be stored at room temperature up to a maximum of 77°F (25°C) in original carton for a maximum single period of 14 days with protection from light and sources of heat. Once SILIQ reaches room temperature, do not place back in refrigerator. Discard after 14 days at room temperature.
Date removed from refrigerator ___/___/___

NDC 0187-0004-01

Contains 1 Single-Dose Prefilled Syringe

SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL
For Subcutaneous Use Only **Rx only**

Each single-dose prefilled syringe delivers 1.5 mL of solution containing brodalumab 210 mg, glutamate (6.5 mg), polysorbate 20 (0.15 mg), proline (36 mg), and Water for Injection.
ATTENTION: Dispense with enclosed medication guide.

SAMPLE - NOT FOR RESALE

VALEANT

XXXXXXX

LOT
EXP

Lot & Exp

Barcode
Human Readable

NDC 0187-0004-01

SILIQ™
(brodalumab)
Injection
210 mg/1.5 mL

For Subcutaneous Use Only

SAMPLE - NOT FOR RESALE

See package insert for dosing information and Instructions for Use.

Carton contents:
- 1 Prefilled Syringe
- 1 Package Insert
- 1 Instructions for Use
- 1 Medication Guide

210 mg/1.5 mL

ATTENTION: Dispense with enclosed medication guide.
Sterile Solution - No Preservative
KEEP OUT OF REACH OF CHILDREN.

Rx only

Contains 1 Single-Dose Prefilled Syringe

BLA 761032 SILIQ® (brodalumab)

Human Interleukin-17 Receptor A (IL-17RA) Antagonist

Valeant Pharmaceuticals North America LLC

400 Somerset Corporate Boulevard, Bridgewater, NJ 08807

Phone: (908) 927-1400

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goal of the SILIQ REMS Program is to mitigate the observed risk of suicidal ideation and behavior, including completed suicides, which occurred in subjects treated with SILIQ by:

- Ensuring that prescribers are educated about the risk of suicidal ideation and behavior observed with SILIQ therapy and the need to counsel patients about this risk.
- Ensuring that patients are informed about the risk of suicidal ideation and behavior observed with SILIQ therapy and the need to seek medical attention for manifestations of suicidal thoughts and behavior, new onset or worsening depression, anxiety, or other mood changes.

II. ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe SILIQ must be certified.

a. To become certified to prescribe SILIQ, prescribers must:
   i. Review the Prescribing Information (PI) for SILIQ.
   ii. Enroll in the SILIQ REMS Program by completing the *SILIQ REMS Program Prescriber Enrollment Form*

b. As a condition of certification, prescribers must:
   i. Enroll each patient in the SILIQ REMS Program by performing the following:
      1) Prior to providing the first prescription, counsel the patient that suicidal ideation and behavior (SIB), including completed suicides, have occurred in patients treated with SILIQ by informing the patient of the following key safety information:
         i. Suicidal ideation and behavior (SIB) events and symptoms may occur at any time during treatment with SILIQ.
         ii. To be aware of symptoms of suicidal ideation and behavior (SIB) events and steps to take if SIB symptoms occur..
      2) Complete the *SILIQ REMS Program Patient-Prescriber Agreement Form* for each patient. Submit the completed form to the SILIQ REMS Program and store a copy in the patient's records.
      3) Provide the patient with the *SILIQ REMS Program Patient Wallet Card*
         i. Understand that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.

ii. Inform SILIQ REMS Program if an enrolled patient has discontinued therapy or is no longer under your care.

c. Valeant Pharmaceuticals North America LLC (Valeant) must:
   i. Ensure that healthcare providers who prescribe SILIQ are certified, in accordance with the requirements described above.
   ii. Provide all the following mechanisms for prescribers to complete the certification process for the SILIQ REMS Program: online, by email, and by fax.
   iii. Ensure that prescribers are notified when they have been certified by the SILIQ REMS Program.
   iv. Maintain a validated, secure database of prescribers who are certified to prescribe SILIQ in the SILIQ REMS Program.
   v. Ensure that prescribers meet the REMS requirements and de-certify prescribers who do not maintain compliance with REMS requirements.
   vi. Ensure that certified prescribers are provided access to the database of certified pharmacies and enrolled patients.
   vii. Provide the *SILIQ REMS Program Prescriber Enrollment Form*, *SILIQ REMS Program Patient-Prescriber Agreement Form*, *SILIQ REMS Program Patient Wallet Card*, and the Prescribing Information to healthcare providers who (1) attempt to prescribe SILIQ and are not yet certified, or (2) inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *SILIQ REMS Program Prescriber Enrollment Form*
- *SILIQ REMS Program Patient-Prescriber Agreement Form*
- *SILIQ REMS Program Patient Wallet Card*

2. Pharmacies that dispense SILIQ must be certified.

a. To become certified to dispense SILIQ, pharmacies must:
   i. Designate an authorized representative to complete the enrollment process by submitting the completed *SILIQ REMS Program Pharmacy Enrollment Form* on behalf of the pharmacy.
   ii. Ensure that the authorized representative oversees implementation and compliance with the SILIQ REMS Program requirements by the following:
      1) Review and complete the *SILIQ REMS Program Pharmacy Enrollment Form.*
      2) Ensure all relevant staff involved in the dispensing of SILIQ are informed of the SILIQ REMS Program requirements as described in the *SILIQ REMS Program Pharmacy Enrollment Form.*
      3) Put processes and procedures in place to ensure the following requirements are completed prior to dispensing SILIQ:
         1. Verify the prescriber is certified and the patient is enrolled in the SILIQ REMS Program by calling the SILIQ REMS Program or by accessing the SILIQ REMS Program Website.

b. As a condition of certification, the certified pharmacies must:

i. Recertify in the SILIQ REMS Program if the pharmacy designates a new authorized representative.
ii. Dispense SILIQ to patients only after obtaining authorization by calling the SILIQ REMS Program or by accessing the SILIQ REMS Program Website. The authorization confirms the following:
    1) The prescriber is certified in the SILIQ REMS Program; and
    2) The patient is enrolled in the SILIQ REMS Program
iii. Maintain documentation that all processes and procedures are in place and are being followed for the SILIQ REMS Program and provide upon request to Valeant, FDA, or a third party acting on behalf of Valeant or FDA.
iv. Comply with audits by Valeant, FDA, or a third party acting on behalf of Valeant or FDA, to ensure that all processes and procedures are in place and are being followed for the SILIQ REMS Program.

c. Valeant must:
    i. Ensure that pharmacies that dispense SILIQ are specially certified, in accordance with the requirements described above.
    ii. Provide all the following mechanisms for pharmacies to complete certification for the SILIQ REMS Program: online, by email, and by fax.
    iii. Ensure that pharmacies are notified when they have been certified by the SILIQ REMS Program.
    iv. Ensure that certified pharmacies are provided access to the database of certified prescribers and enrolled patients.
    v. Verify every year that the authorized representative's name and contact information correspond to those of the currently designated authorized representative for the certified pharmacy. If different, the pharmacy must be required to recertify with a new authorized representative.

The following materials are part of the REMS and are appended:

- *SILIQ REMS Program Pharmacy Enrollment Form*
- *SILIQ REMS Program Website* (www.SILIQREMS.com)

3. SILIQ must be dispensed to patients with evidence or other documentation of safe-use conditions.

a. To become enrolled in the SILIQ REMS Program, a patient must sign a *SILIQ REMS Program Patient-Prescriber Agreement Form* indicating that he/she has:
    i. Received and has read the SILIQ *REMS Program Patient-Prescriber Agreement Form* with their healthcare provider.
    ii. Received counseling from the prescriber regarding:
        1) the observed risk of suicidal ideation and behavior (SIB)
        2) the importance of keeping the *SILIQ REMS Program Patient Wallet Card* with them at all times
        3) the need to seek medical attention should they experience emergence or worsening of suicidal ideation and behavior
    iii. Received the *SILIQ REMS Program Patient Wallet Card*

b. Valeant must:
    i. Provide all of the following mechanisms for the certified prescribers to be able to submit the completed *SILIQ REMS Program Patient-Prescriber Agreement Form* to the SILIQ REMS Program: online, by email, and by fax.

The following materials are part of the REMS and are appended:

- *SILIQ REMS Program Patient Wallet Card*
- *SILIQ REMS Program Patient-Prescriber Agreement Form*

B. Implementation System

1. Valeant must ensure that SILIQ is only distributed to certified pharmacies by:

    a. Ensuring that wholesalers/distributors who distribute SILIQ comply with the program requirements for wholesalers/distributors. The wholesalers/distributor must:

        i. Put processes and procedures in place to verify, prior to distributing SILIQ, that the pharmacies are certified.
        ii. Train all relevant staff on the SILIQ REMS Program requirements.
        iii. Comply with audits by Valeant, FDA, or a third party acting on behalf of Valeant or FDA to ensure that all processes and procedures are in place and are being followed for the SILIQ REMS Program. In addition, wholesalers/distributors must maintain documentation to support that all processes and procedures are in place, being followed, and make the documentation available for audits.
        iv. Provide distribution data to Valeant to verify compliance with the REMS.

    b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of SILIQ and provide the data to Valeant.

2. Valeant must monitor distribution data to ensure all the processes and procedures are in place and functioning to support the requirements of the SILIQ REMS Program.

3. Valeant must audit the wholesalers/ distributors within 90 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the SILIQ REMS Program.

4. Valeant must maintain a validated, secure database of prescribers and pharmacies that are certified to dispense SILIQ in the SILIQ REMS Program.

5. Valeant must maintain a validated, secure database of patients who are enrolled in the SILIQ REMS Program.

6. Valeant must maintain records of SILIQ certified prescribers, certified pharmacies, and enrolled patients to meet REMS requirements.

7. Valeant must maintain a SILIQ REMS Program Call Center (855-511-6135) and SILIQ REMS Program Website (www.SILIQREMS.com). The REMS Program Website must include the capability to confirm patient authorization status, and the option to print the Prescribing Information, Medication Guide, and SILIQ REMS materials. The SILIQ product website must include a prominent REMS-specific link to the

SILIQ REMS Program Website. The SILIQ REMS Program Website must not link back to the product website(s).

8. Valeant must ensure that the SILIQ REMS Program Website is fully operational, including the capability to complete prescriber and pharmacy certification and patient enrollment online; online confirmation of patient authorization functionality; and the REMS materials listed in or appended to the SILIQ REMS document are available through the SILIQ REMS Program Website and by calling the SILIQ REMS Program Call Center.

9. Valeant must monitor on an ongoing basis the certified pharmacies to ensure the requirements of the SILIQ REMS Program are being met. Valeant must institute corrective action if noncompliance is identified and decertify pharmacies that do not maintain compliance with the REMS requirements.

10. Valeant must maintain an ongoing annual audit plan that involves certified pharmacies.

11. Valeant must audit 20% or one, whichever is greater, of the certified pharmacies within 90 calendar days after the pharmacy places its first order of SILIQ to ensure that all processes and procedures are in place and functioning to support the requirements of the SILIQ REMS Program. The certified pharmacies must be identified in Valeant's ongoing annual audit plan. Valeant must institute corrective action if noncompliance is identified.

12. Valeant must take reasonable steps to improve implementation of and compliance with the requirements in the SILIQ REMS Program based on monitoring and evaluation of the SILIQ REMS Program.

III. Timetable for Submission of Assessments

Valeant must submit REMS assessments to the FDA at 6 months and 12 months and annually thereafter from the date of the initial approval of the REMS (February 15, 2017). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Valeant must submit each assessment so that it will be received by the FDA on or before the due date.

SILIQ™
(brodalumab) injection
210 mg/1.5 mL

SILIQ™ REMS Program
Prescriber Enrollment Form

Instructions

Please fax this completed form to the SILIQ Risk Evaluation Mitigation Strategy (REMS) Program at 1-866-227-9451, submit online at www.SILIQREMS.com, or email it to SILIQ@SILIQREMS.com.

SILIQ (brodalumab) is available only through the SILIQ REMS Program. The SILIQ REMS Program is available to answer questions regarding this program and initiating treatment with SILIQ. Please call 1-855-511-6135 for more information.

Only prescribers, pharmacies, and patients enrolled in the SILIQ REMS Program are able to prescribe, dispense and receive SILIQ.

1. Review the one-time SILIQ REMS Enrollment Information for Prescribers, including the Prescribing Information (PI).
2. Complete and submit this *SILIQ REMS Program Prescriber Enrollment Form* via the program website, email, or the fax number provided.
3. Send your patient's prescription to a pharmacy that is enrolled in the SILIQ REMS Program by utilizing the Pharmacy Certification Look Up function on the SILIQ REMS Program website.

You will receive enrollment confirmation via your preferred method of communication (email or fax) within 2 business days.

SILIQ Prescriber Information (*Required)

First Name*:	Last Name*:	Degree*: ❒ MD ❒ DO ❒ PA ❒ NP ❒ Other
National Provider Identification (NPI) Number*:	DEA Number:	
Name of Institution or Healthcare Facility*:		Specialty*:
Street Address*:		
City*:	State*:	Zip Code*:
Office Phone Number*:	Office Fax Number*:	Mobile Phone Number:
Email Address:	Preferred Method of Communication*: ❒ Email ❒ Fax	

Prescriber Agreement

By completing this form, I attest that:

1. I have read and understand the SILIQ Prescribing Information.
2. I understand that I must comply with the Program requirements in order to prescribe SILIQ.
3. I understand that by signing this *SILIQ REMS Program Prescriber Enrollment Form* (one time only), I will be enrolled in the SILIQ REMS Program and may prescribe SILIQ.
4. I understand that, prior to authorizing the first prescription, I am responsible for counseling each patient that suicidal ideation and behavior (SIB), including completed suicides, have occurred in patients treated with SILIQ. I will inform the patient of the following key safety information:
   - Suicidal ideation and behavior (SIB) events and symptoms may occur at any time during treatment with SILIQ.
   - To be aware of symptoms of suicidal ideation behavior (SIB) events and steps to take if SIB symptoms occur.
5. I understand that I must submit a completed *SILIQ REMS Program Patient-Prescriber Agreement Form* for each patient before I prescribe SILIQ for the first time, and store a copy of the completed form in the patient's record.
6. I will provide each patient with a *SILIQ REMS Program Patient Wallet Card* and instruct each patient to carry this card with them at all times.
7. I understand that patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.
8. I will inform the SILIQ REMS Program if an enrolled patient has discontinued therapy or is no longer under my care.
9. I understand Valeant and its agents may contact me via phone, mail, fax, email, or in person to support administration of the SILIQ REMS Program.

Prescriber Signature*:	Date*:

Reference ID: 4067005

SILIQ™
(brodalumab) injection
210 mg/1.5 mL

SILIQ™ REMS Program
Patient-Prescriber Agreement Form

Instructions for Prescribers

1. Sign this form along with your patient and place it in the patient's chart.
2. Tear off the bottom portion and provide it to your patient to take home as a reference.
3. Submit this completed form to the SILIQ Risk Evaluation and Mitigation Strategy (REMS) Program online at www.SILIQREMS.com or by fax at 1-866-227-9451.

Patient Acknowledgement (*Required)

By signing this form, I acknowledge that:

☐ I understand that suicidal thoughts and behavior, including completed suicides, have occurred in patients treated with SILIQ.

☐ I will call my doctor or the **National Suicide Prevention Lifeline at 1-800-273-8255** if:

- I feel new or worsening feelings of withdrawal, depression, anxiety, hopelessness, or other mood changes beginning.
- I am thinking about hurting or killing myself; seeking access to firearms, pills or other means for the purpose of self-harm; or am talking or writing about death and dying.

☐ I will **call 911** if I feel an **immediate threat of death or self-injury**.

☐ My doctor has given me a *SILIQ REMS Patient Wallet Card* to carry with me at all times.

Printed First and Last Name*		Date of Birth (Month/Day/Year):*
Phone Number*:	State*:	Zip Code:*
Patient Signature*:		Date:*

Prescriber Acknowledgement

I acknowledge that prior to prescribing SILIQ:

☐ I have counseled my patient about the importance of seeking medical advice should signs of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes emerge.

☐ I have evaluated the risks and benefits of continuing treatment with SILIQ if such events occur.

Printed First and Last Name:*		
Phone Number*	DEA:	NPI*
Prescr ber Signature*		Date:*

SILIQ™
(brodalumab) injection
210 mg/1.5 mL

SILIQ Patient Information

- I understand that suicidal thoughts and behavior, including completed suicides, have occurred in patients treated with SILIQ.
- I will call my doctor or the **National Suicide Prevention Lifeline at 1-800-273-8255** if:
  - I feel new or worsening feelings of withdrawal, depression, anxiety, hopelessness, or other mood changes beginning.
  - I am thinking about hurting or killing myself; seeking access to firearms, pills or other means for the purpose of self-harm; or am talking or writing about death and dying.
- I will **call 911** if I feel an **immediate threat of death or self-injury**.

For more information about the SILIQ REMS Program please visit www.SILIQREMS.com

Reference ID: 4067005

SILIQ™
(brodalumab) injection
210 mg/1.5 mL

SILIQ™ REMS Program
Pharmacy Enrollment Form

Instructions

To become enrolled, the pharmacy must designate an Authorized Pharmacy Representative to ensure compliance with the SILIQ Risk Evaluation and Mitigation Strategy (REMS) Program.

Please fax this completed form to the SILIQ REMS Program at 1-866-227-9451, submit online at www.SILIQREMS.com, or email it to SILIQ@SILIQREMS.com.

SILIQ (brodalumab) is available only through the SILIQ REMS Program. The SILIQ REMS Program is available to answer questions regarding this program and initiating treatment with SILIQ. Please call 1-855-511-6135 for more information.

Authorized Pharmacy Representative Responsibilities

I am the authorized representative designated by my pharmacy to coordinate the activities of the SILIQ REMS Program. By signing this form, I agree, on behalf of myself and my pharmacy, to comply with the following program requirements:

1. I understand that by signing this form, and upon confirmation from the SILIQ REMS Program, this pharmacy will be enrolled in the SILIQ REMS Program, and will be able to order and dispense SILIQ.
2. This pharmacy will re-enroll in the SILIQ REMS Program if the name and contact information for the Authorized Pharmacy Representative changes.
3. This pharmacy will ensure that all relevant staff involved in the dispensing of SILIQ is trained on the SILIQ REMS Program requirements.
4. This pharmacy will maintain and make available appropriate documentation reflecting that all processes and procedures are in place and being followed.
5. I understand that non-compliance with the requirements of the SILIQ REMS Program will result in decertification of my pharmacy and termination of authorization to dispense SILIQ.
6. I will ensure that, prior to dispensing SILIQ, my pharmacy will verify that the prescriber is certified and the patient is enrolled to receive SILIQ by contacting the SILIQ REMS Program.
7. This pharmacy will comply with audits by Valeant, the US Food and Drug Administration (FDA), or a designated third party acting on behalf of Valeant or FDA to ensure compliance with the SILIQ REMS Program.

Pharmacy Information (*Required)

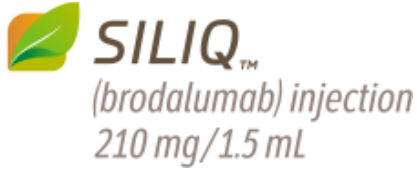
Pharmacy Name*:		Pharmacy Type*: ❒ Inpatient ❒ Outpatient	
Address*:		City*:	State*: Zip Code*:
Pharmacy Identifier* (at least one required):	NPI:	NCPDP:	DEA:

Authorized Pharmacy Representative Information (*Required)

First Name*:	Last Name*:	MI:
Telephone Number*:	Alternate Telephone Number:	Office Fax*:
Email*:	Preferred Method of Communication*: ❒ Email ❒ Fax	
Authorized Pharmacy Representative Signature*:		Date*:

By completing and submitting this form and receiving enrollment confirmation, your pharmacy will be certified in the SILIQ REMS Program. You will receive confirmation of your enrollment via your preferred method of communication.

Reference ID: 4067005



SILIQ™ REMS Program
Patient Wallet Card

SILIQ is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

WARNING: Suicidal thoughts and behavior, including completed suicides, have occurred in patients treated with SILIQ.

Taking SILIQ has proven effective for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. However, if you are experiencing sudden feelings of withdrawal, anxiety, depression or hopelessness, call your doctor immediately. Suicide warning signs also include thinking about hurting or killing yourself; seeking access to firearms, pills or other means for the purpose of self-harm; and talking or writing about death and dying when these actions are out of the ordinary.[1,2]

You are not alone. Help is available.

I will call my doctor or the **National Suicide Prevention Lifeline at 1-800-273-8255 (TALK)** if:

- I feel new or worsening feelings of withdrawal, depression, anxiety, hopelessness, or other mood changes beginning.
- I am thinking about hurting or killing myself; seeking access to firearms, pills or other means for the purpose of self-harm; or am talking or writing about death and dying[2].

I will **call 911** if I feel an **immediate threat of death or self-injury**.

Learn about the signs of suicide at www.suicidelifeline.org.

For more information, visit www.SILIQREMS.com or call 1-855-511-6135.

[1] American Association of Suicidology. Know the Warning Signs of Suicide. http://www suicidology.org/resources/warning-signs.
[2] American Foundation for Suicide Prevention. Suicide Warning Signs. http //www.afsp.org/understanding-suicide/suicide-warning-signs.

Reference ID: 4067005

SILIQ REMS Program
Website Screen Captures

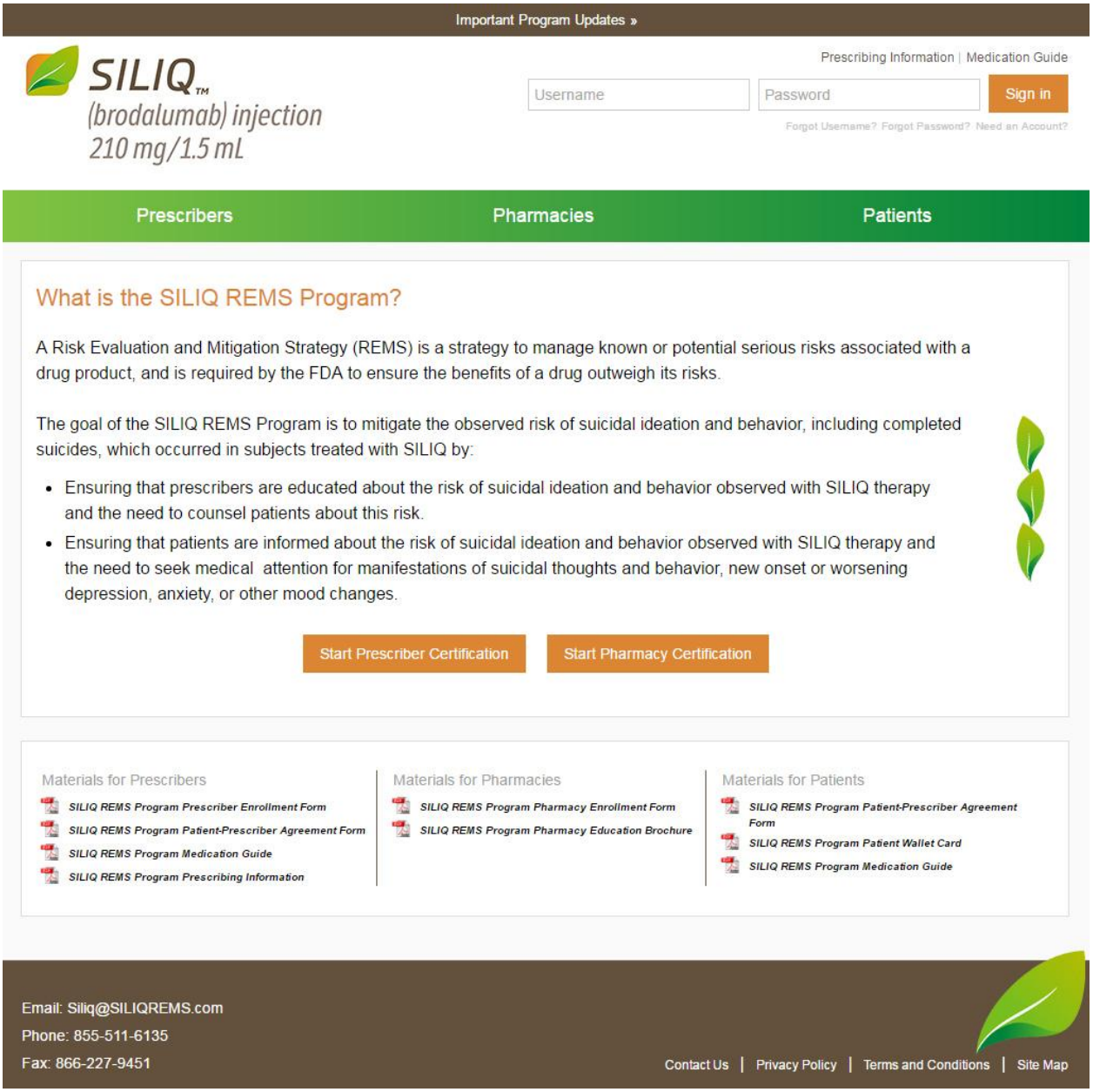
February 13th, 2017

Version 5.0

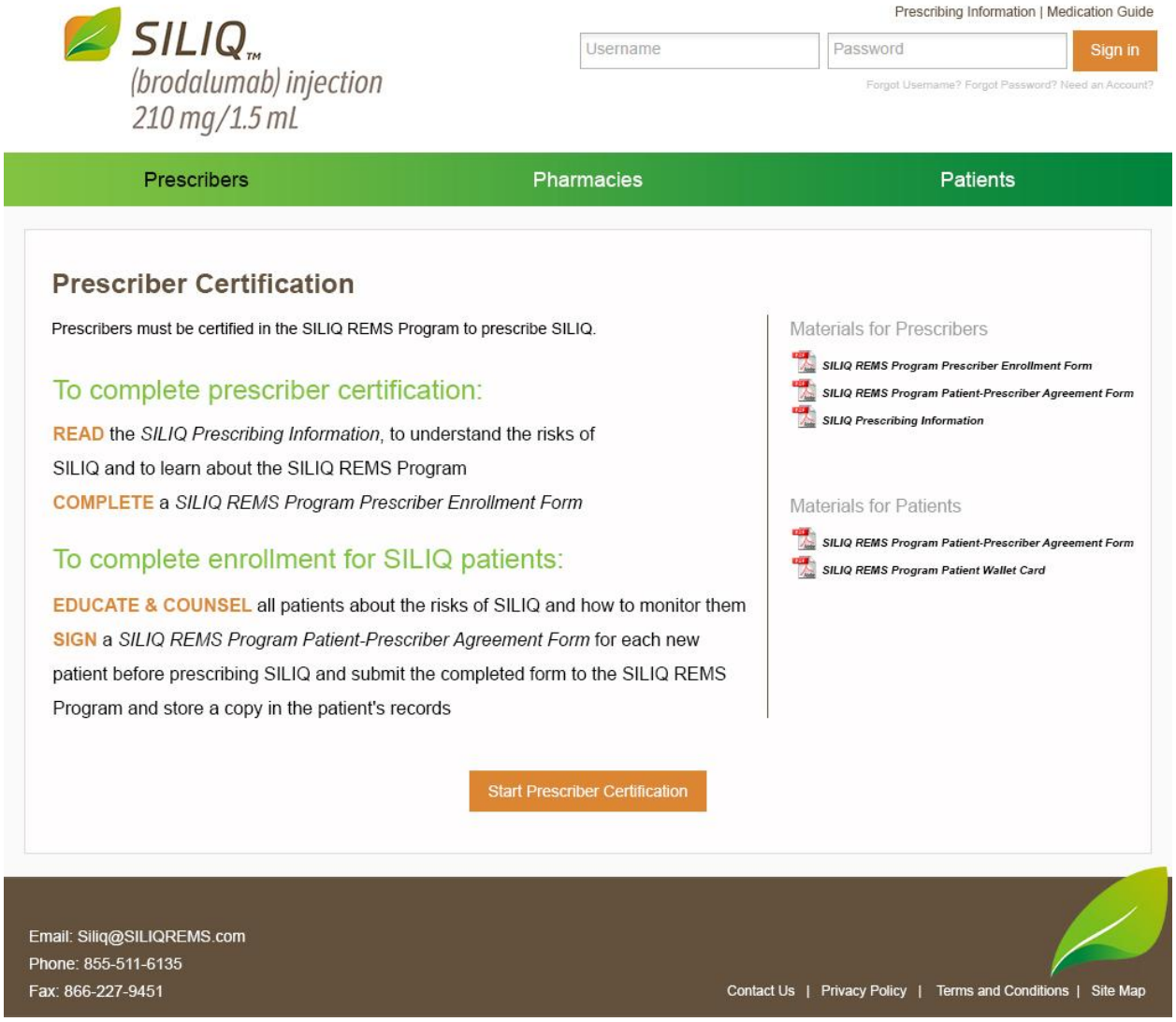
Table of Contents

1. General Pages

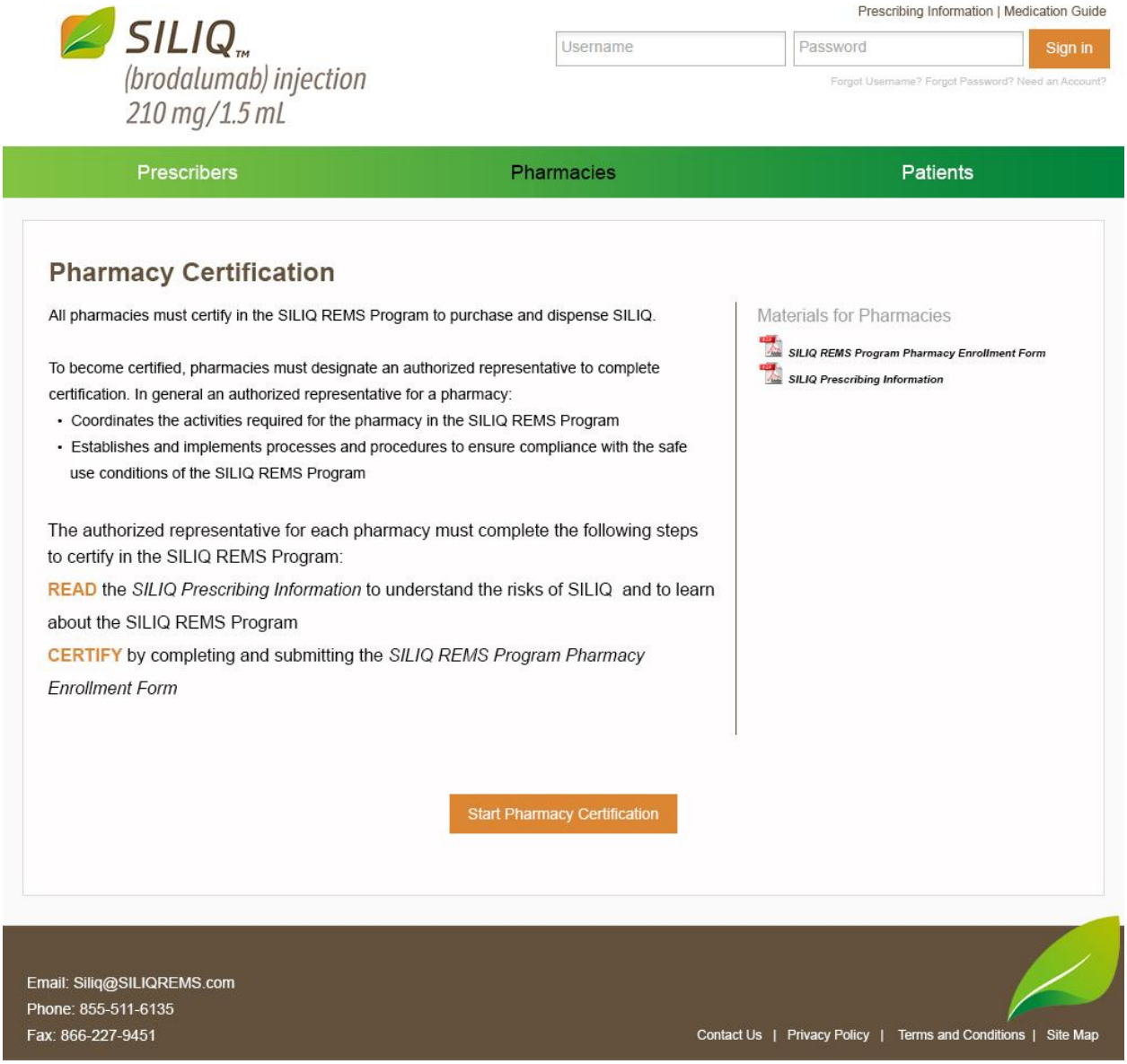
1.1 Home Page



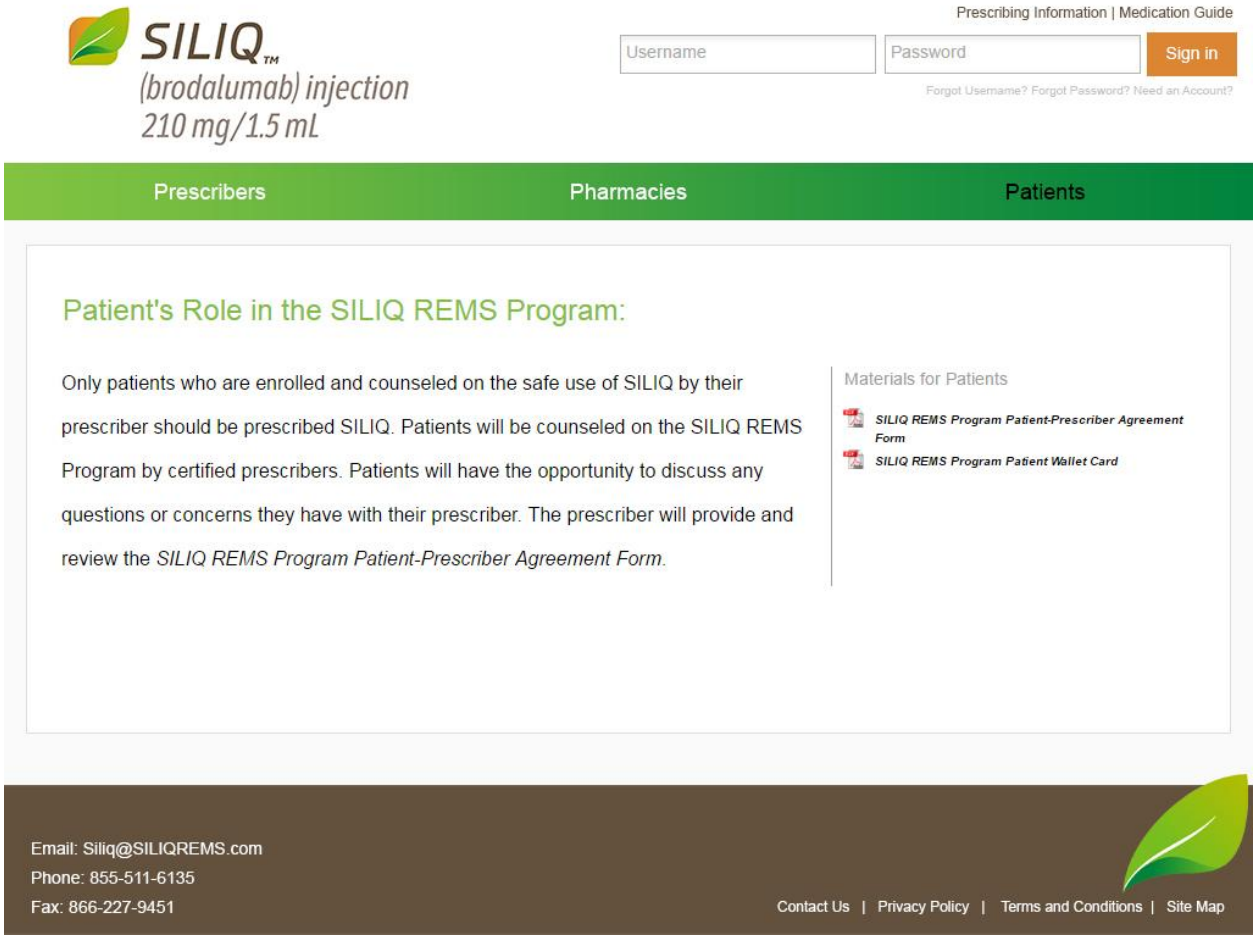
1.2 Prescriber Landing Page



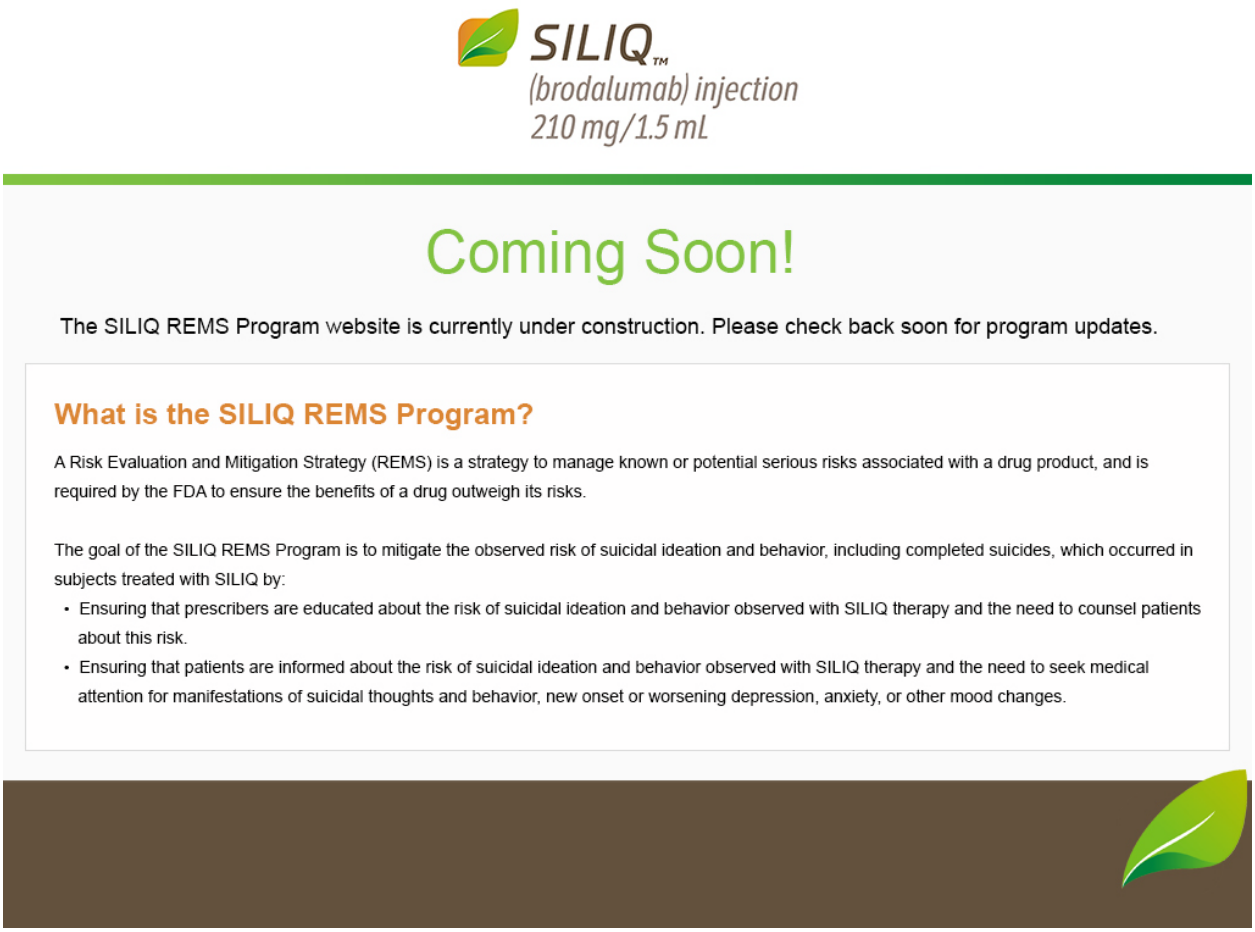
1.3 Pharmacy Landing Page



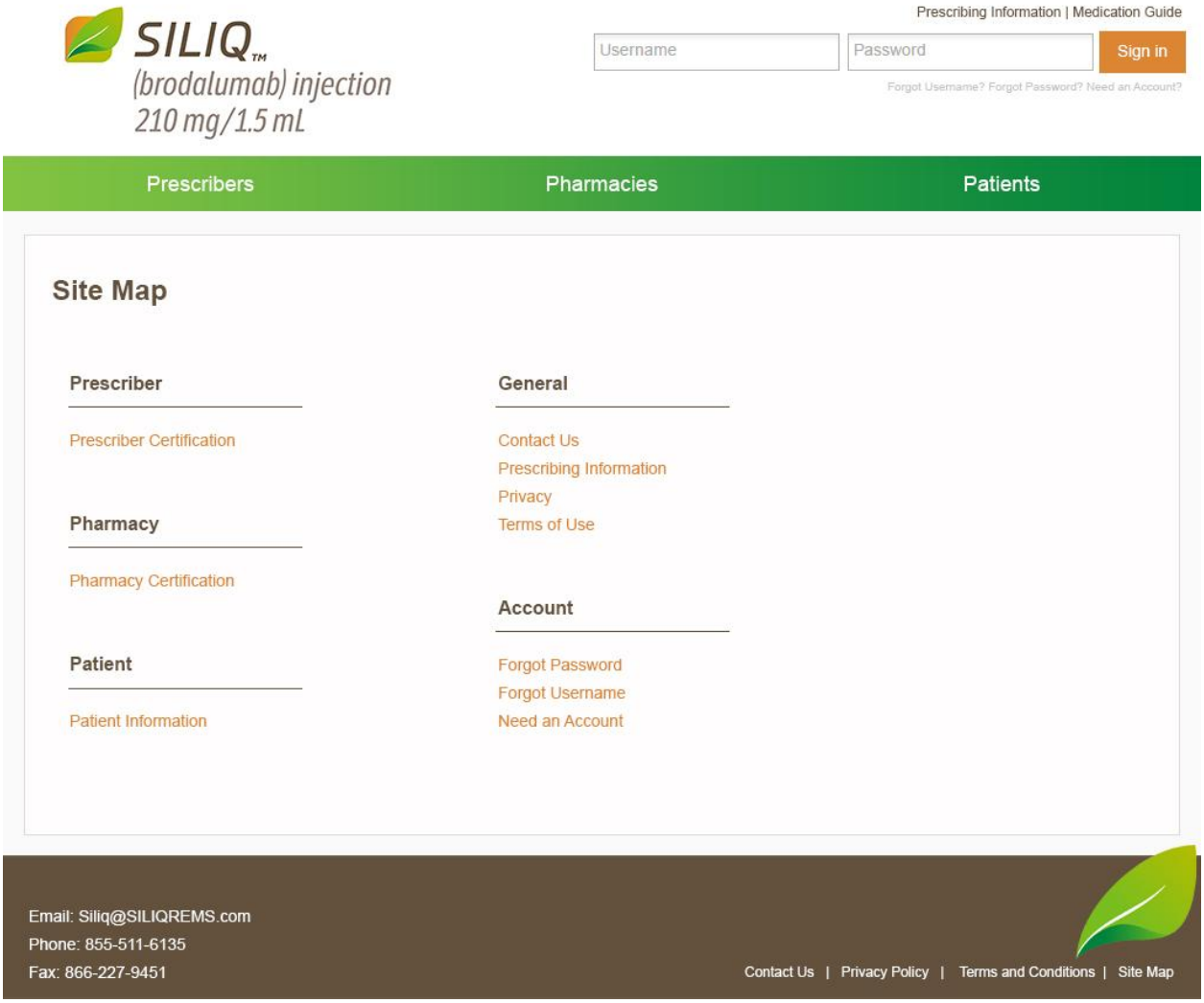
1.4 Patient Landing Page



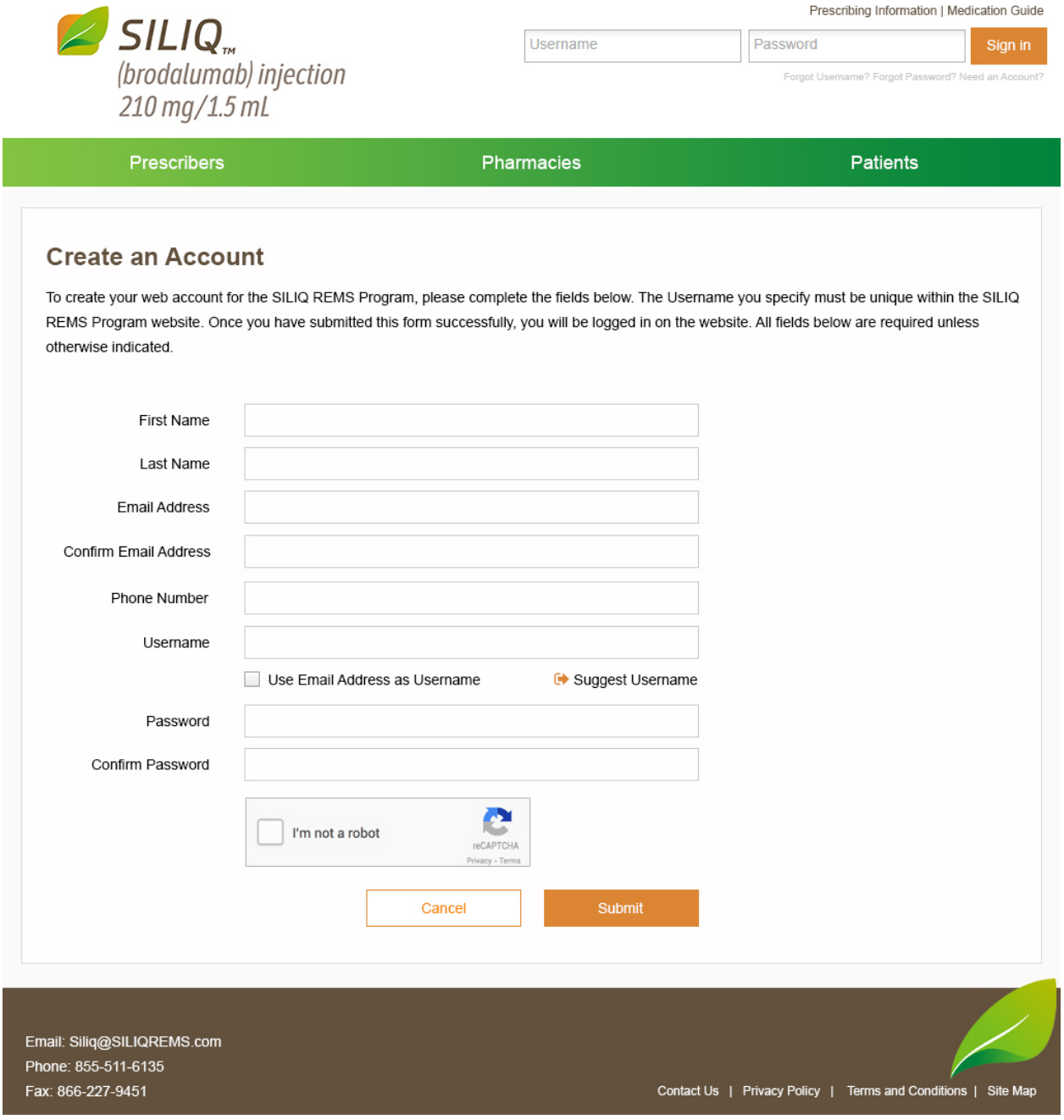
1.5 Coming Soon Page



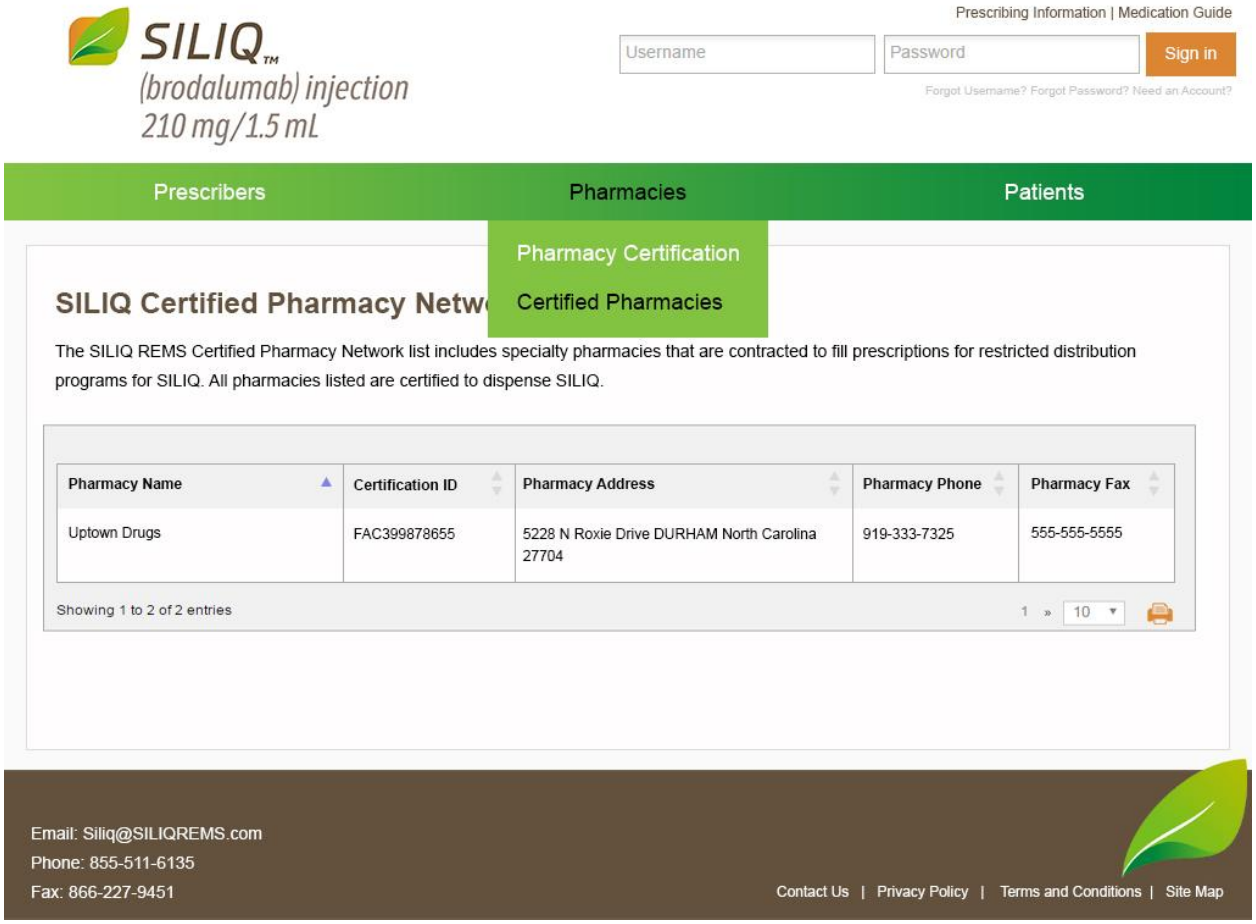
1.6 Site Map


SILIQ™
(brodalumab) injection
210 mg/1.5 mL
Prescribing Information | Medication Guide
Username
Password
Sign in
Forgot Username? Forgot Password? Need an Account?
Prescribers
Pharmacies
Patients
Site Map
Prescriber
Prescriber Certification
Pharmacy
Pharmacy Certification
Patient
Patient Information
General
Contact Us
Prescribing Information
Privacy
Terms of Use
Account
Forgot Password
Forgot Username
Need an Account
Email: Siliq@SILIQREMS.com
Phone: 855-511-6135
Fax: 866-227-9451
Contact Us | Privacy Policy | Terms and Conditions | Site Map

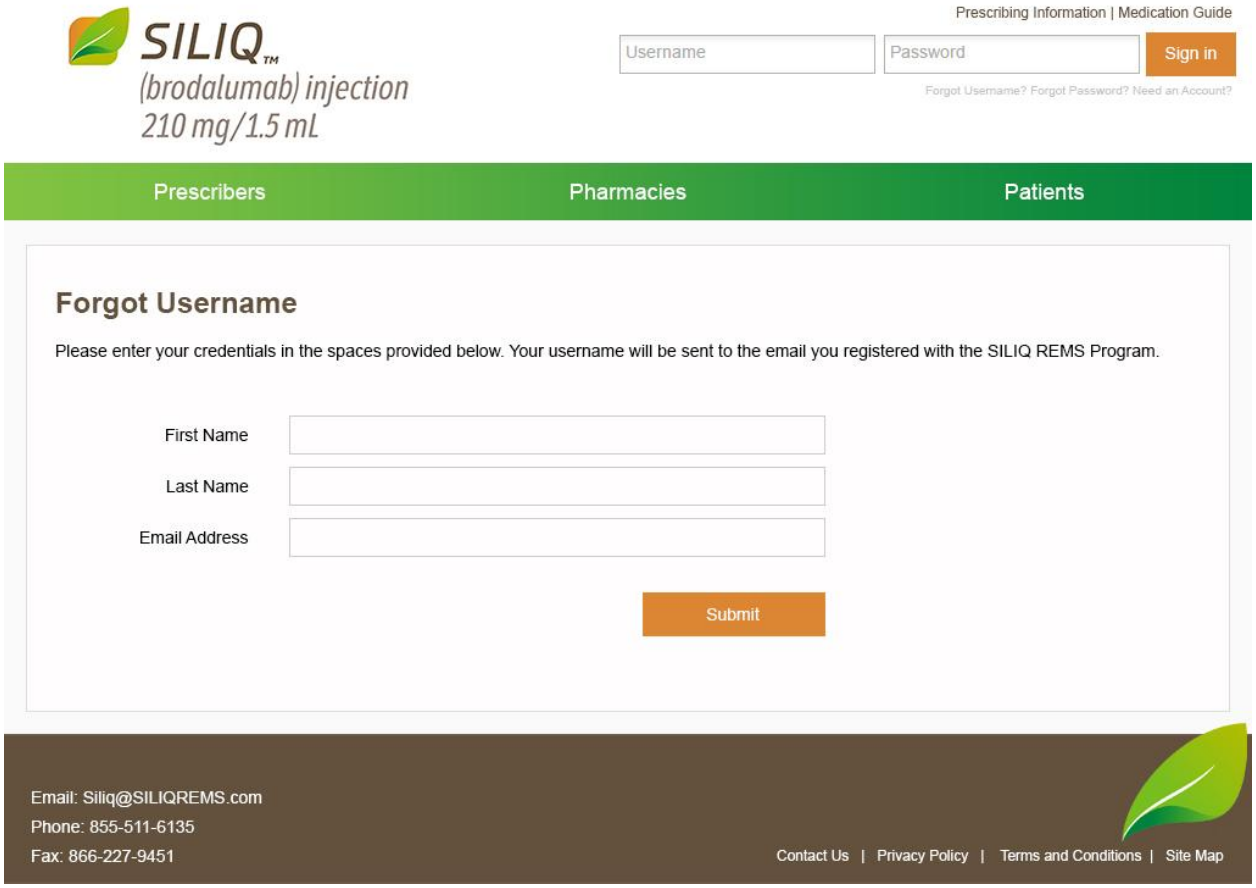
1.7 Account Registration Page



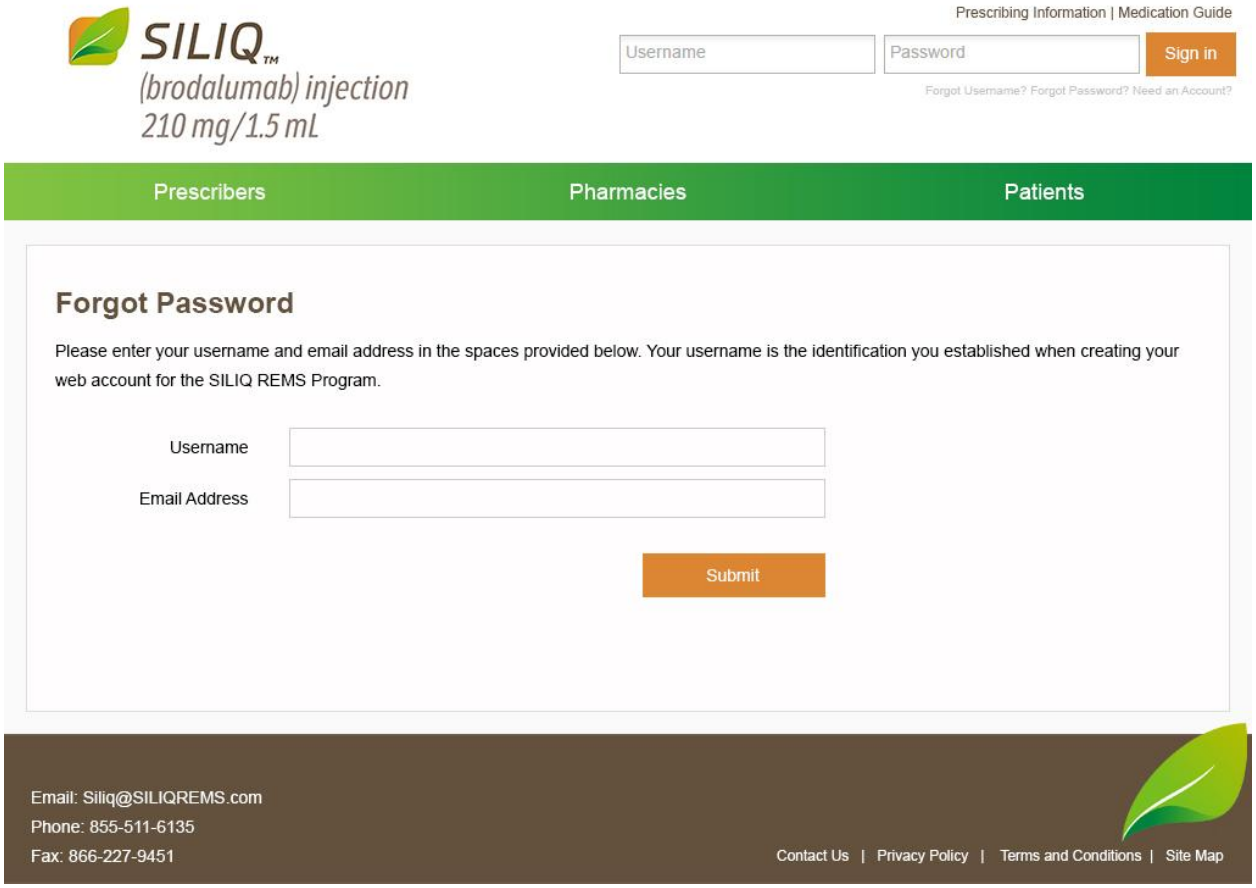
1.8 Certified Pharmacies



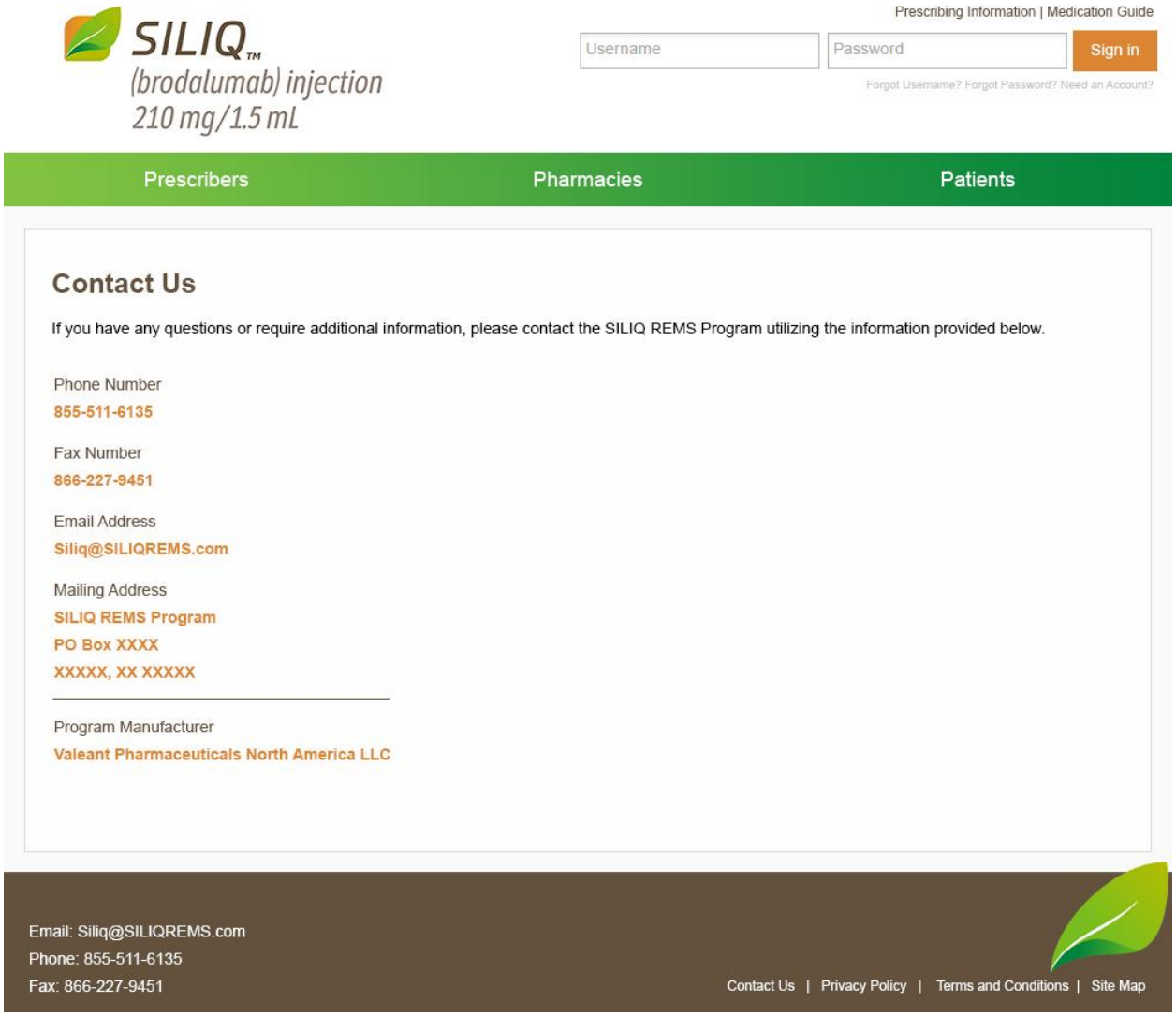
1.9 Forgot Username



1.10 Forgot Password

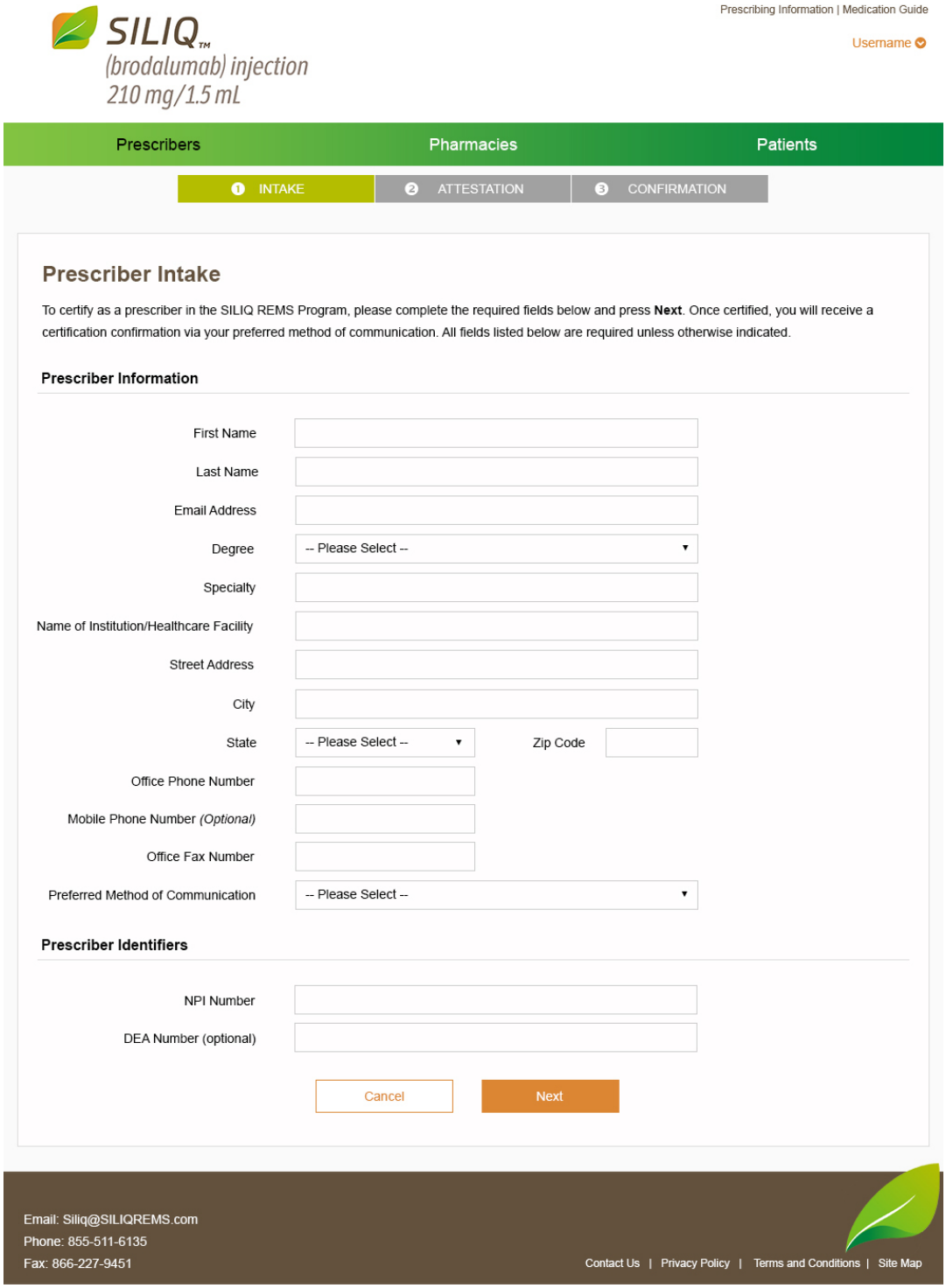


1.11 Contact Us

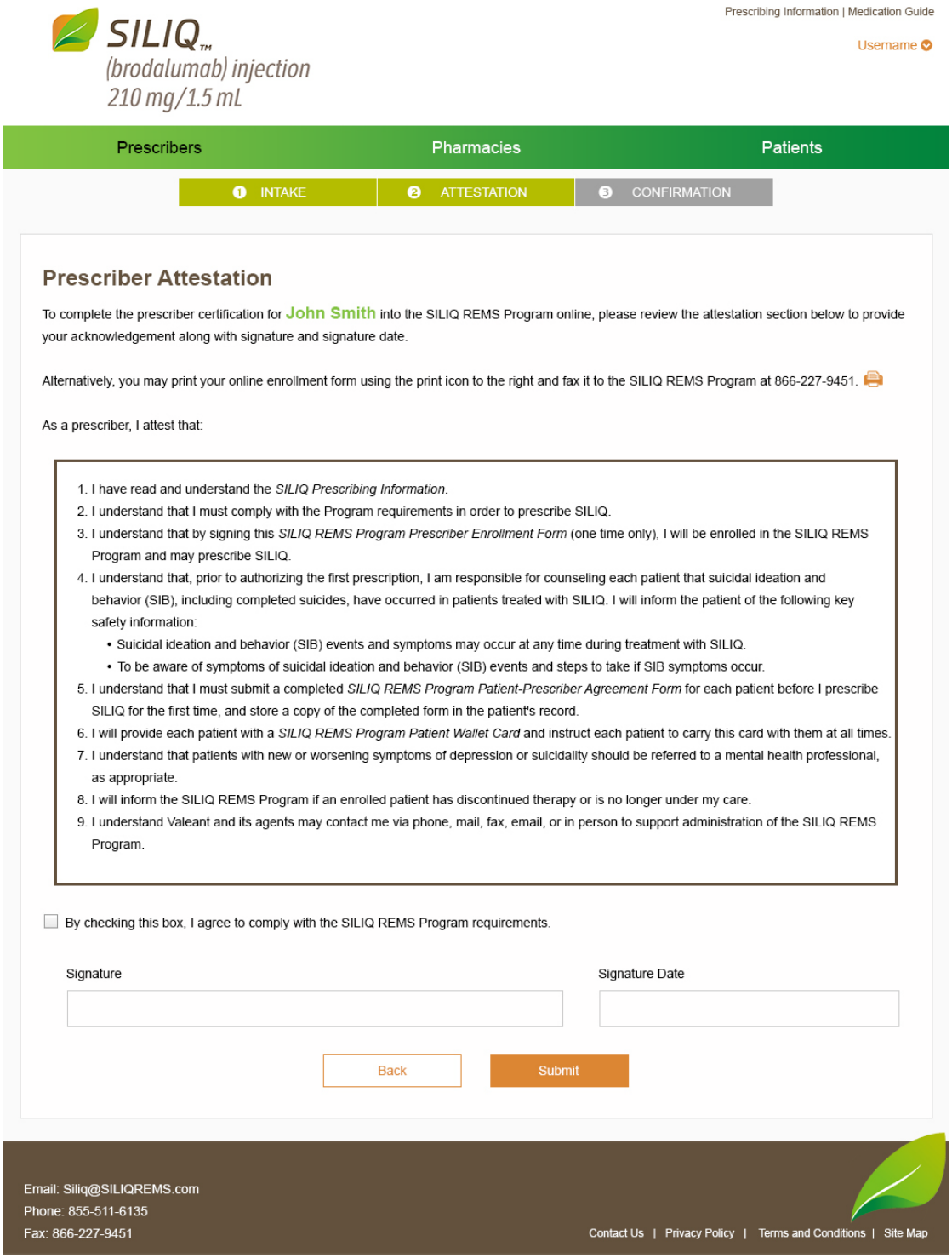


2. Prescriber Online Certification

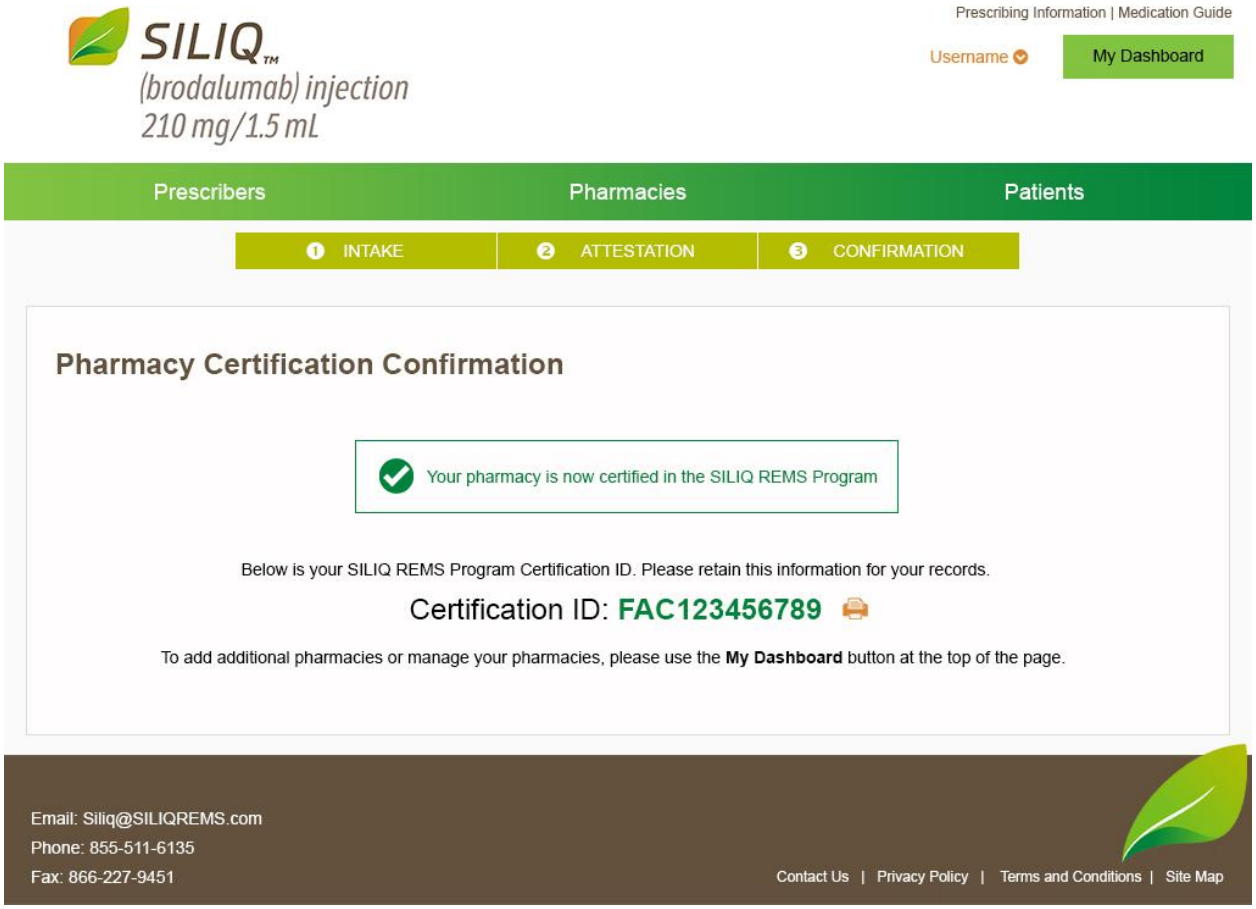
2.1 Prescriber Information Page



2.2 Prescriber Attestation Page

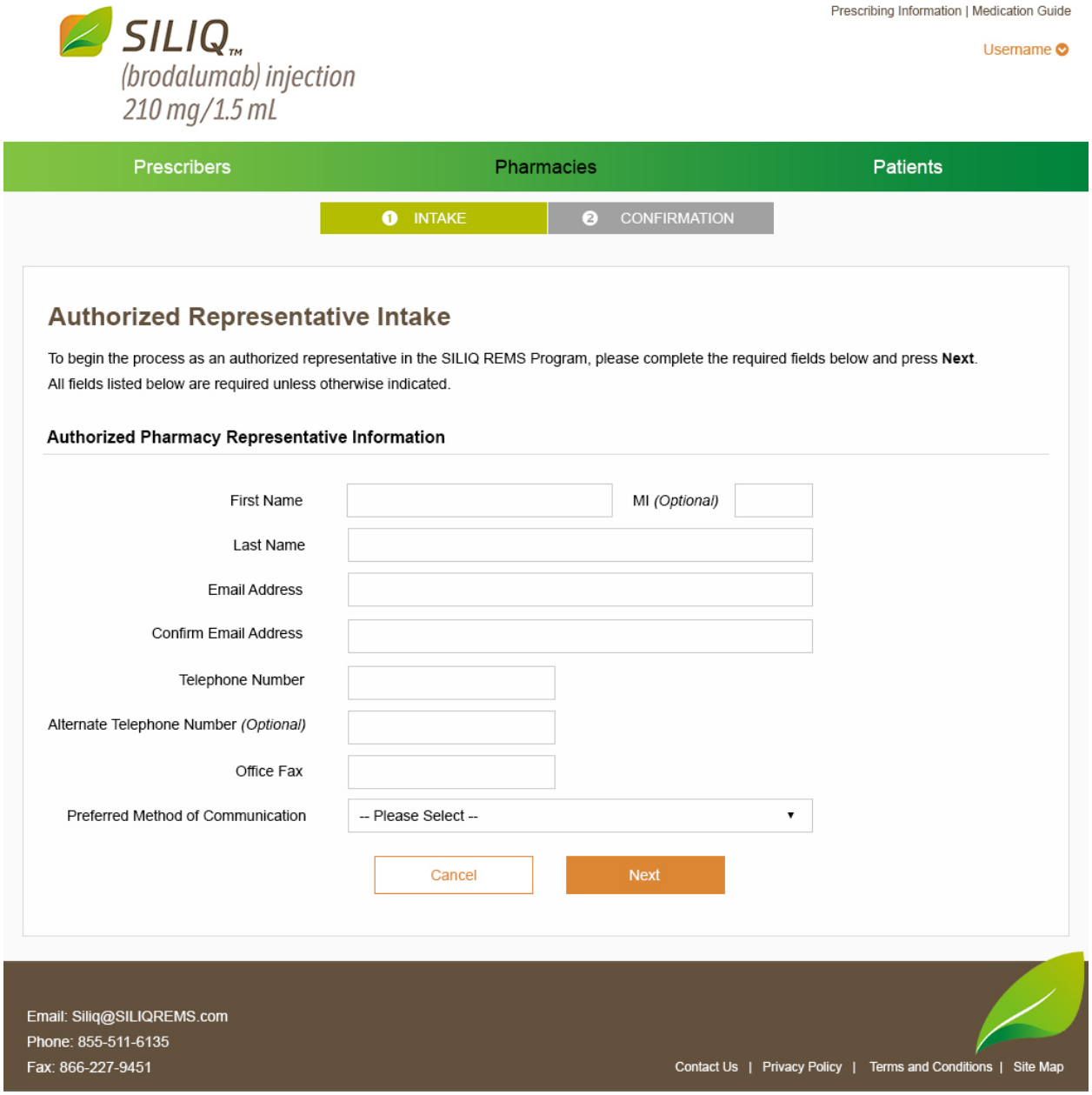


2.3 Prescriber Confirmation Page

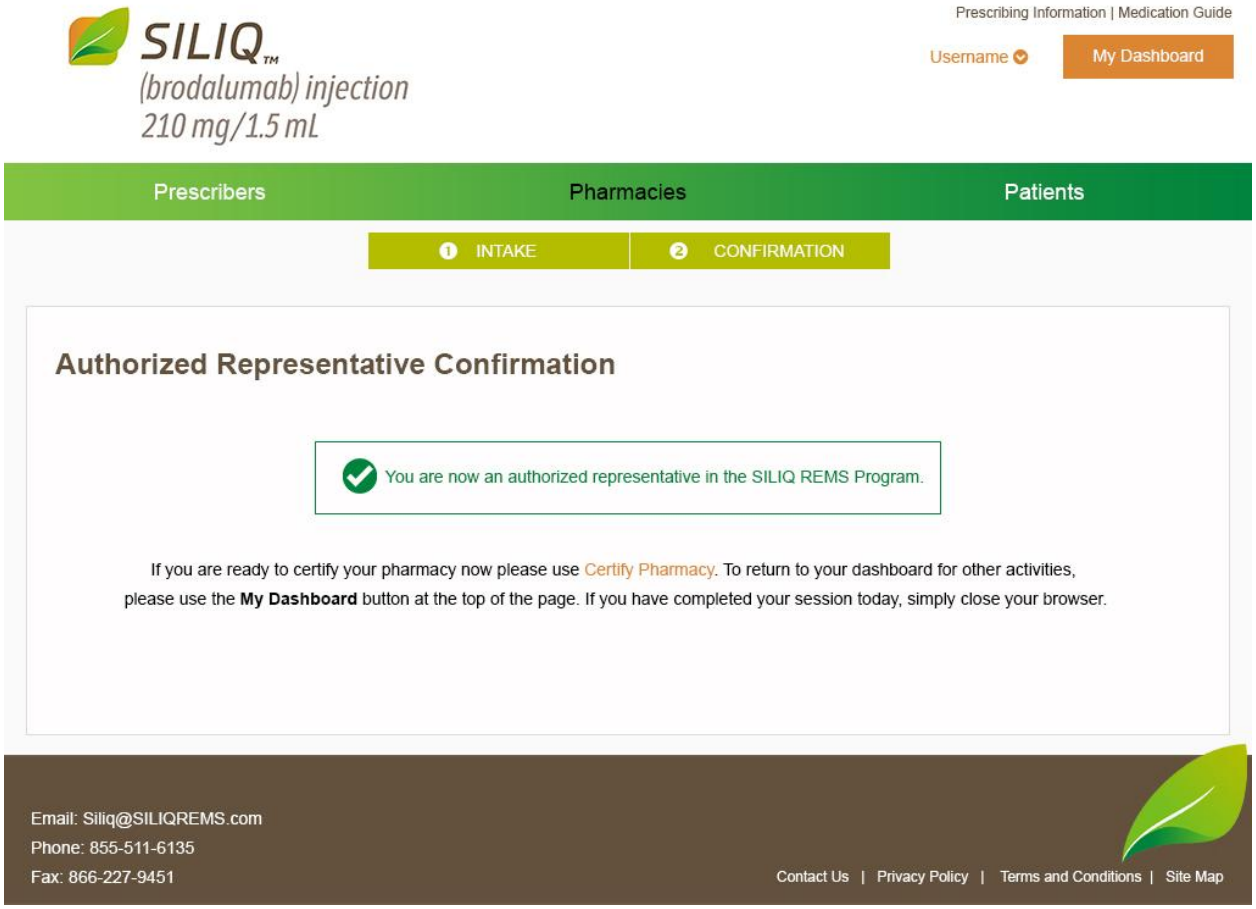


3. Pharmacy Online Certification

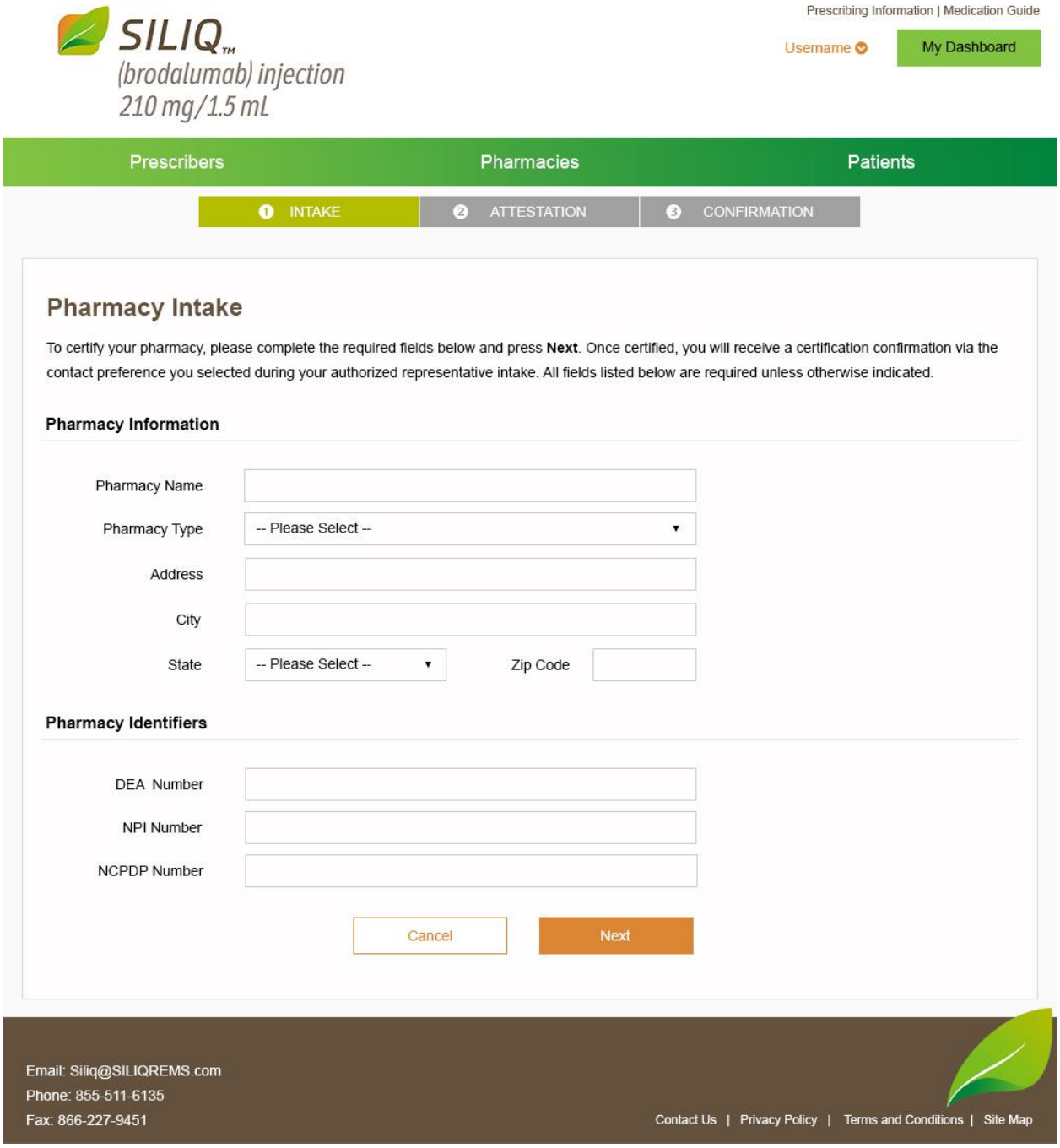
3.1 Authorized Representative Information Page



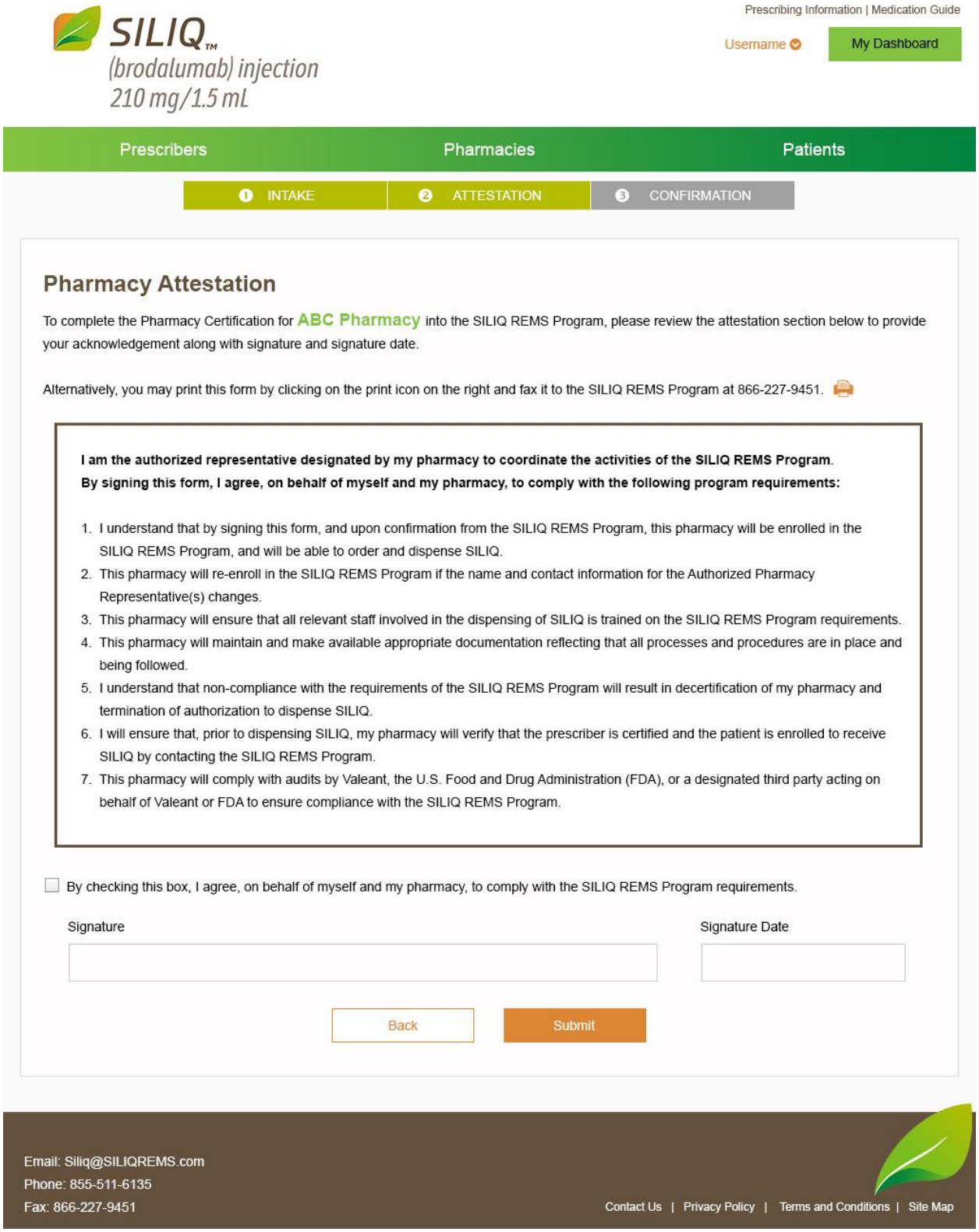
3.2 Authorized Representative Confirmation Page



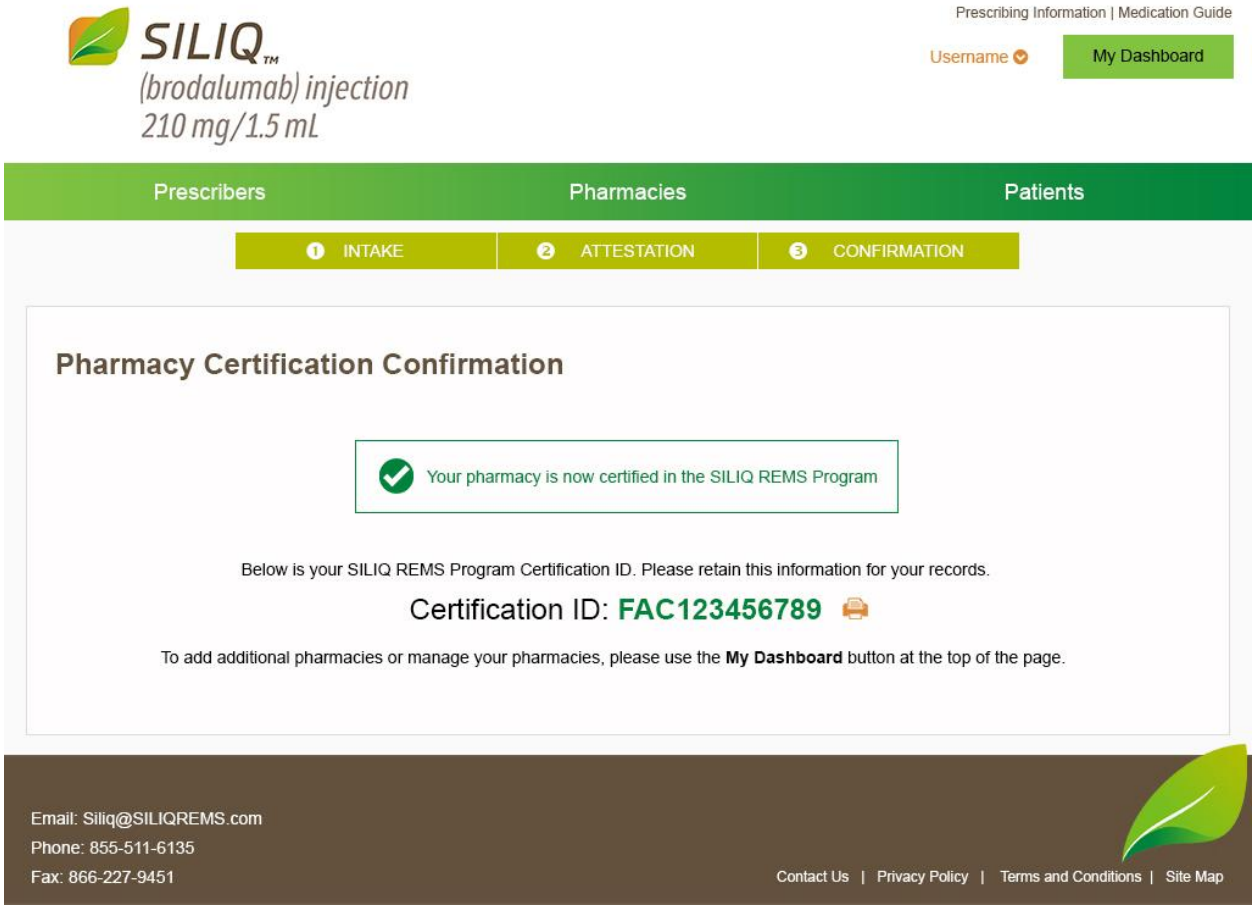
3.3 Pharmacy Information Page



3.4 Pharmacy Attestation Page

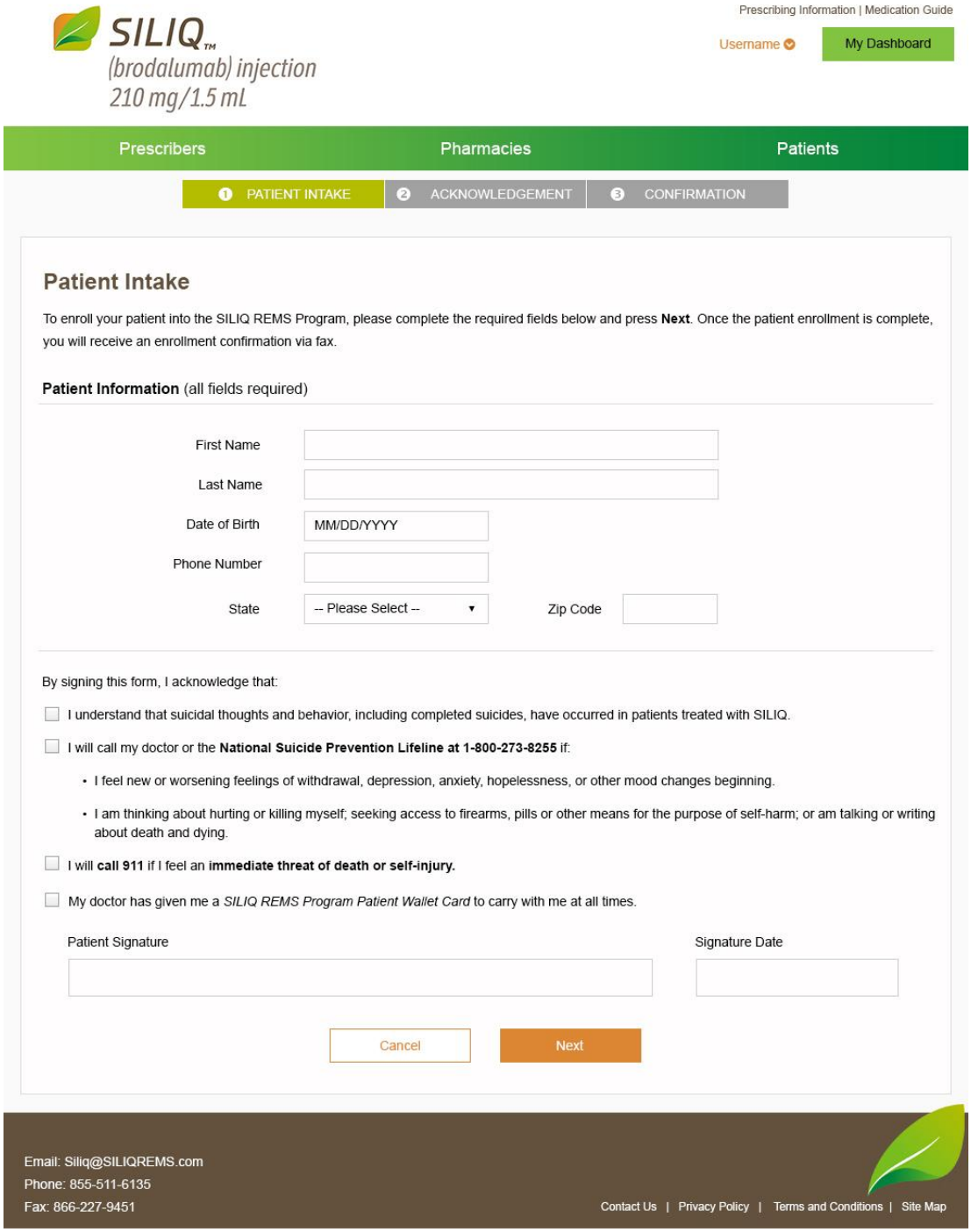


3.5 Pharmacy Confirmation Page

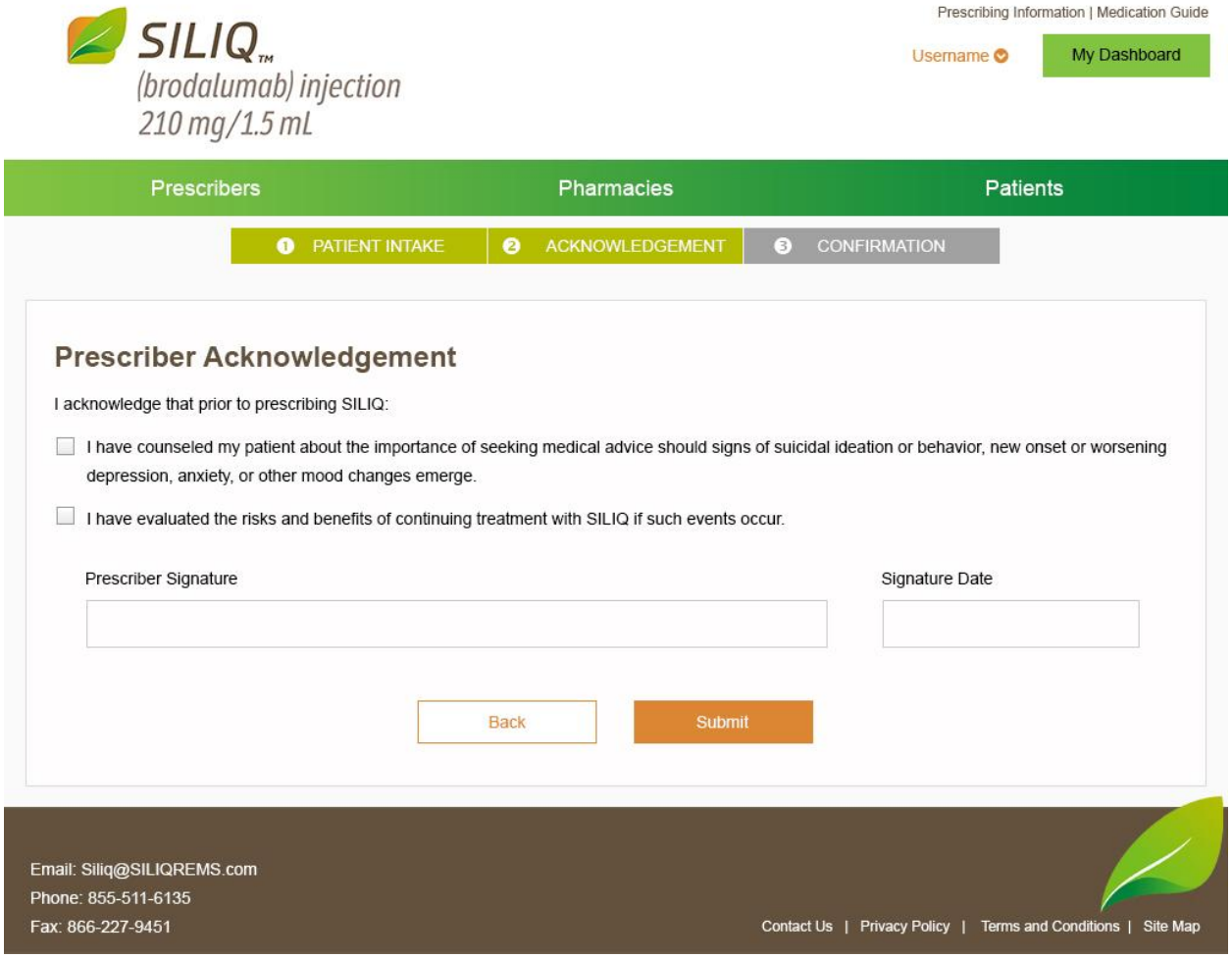


4. Patient Online Enrollment

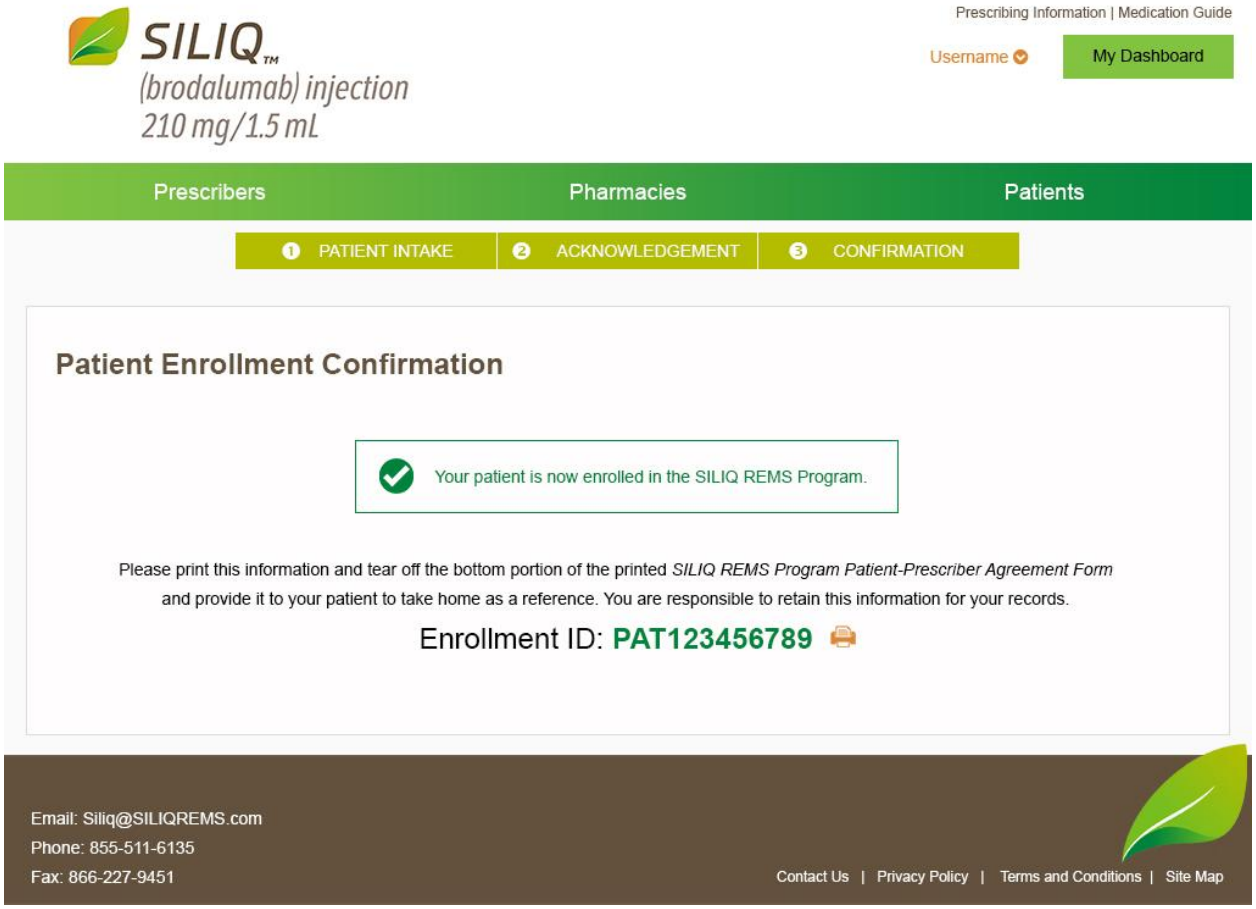
4.1 Patient Information Page



4.2 Prescriber Acknowledgment Page

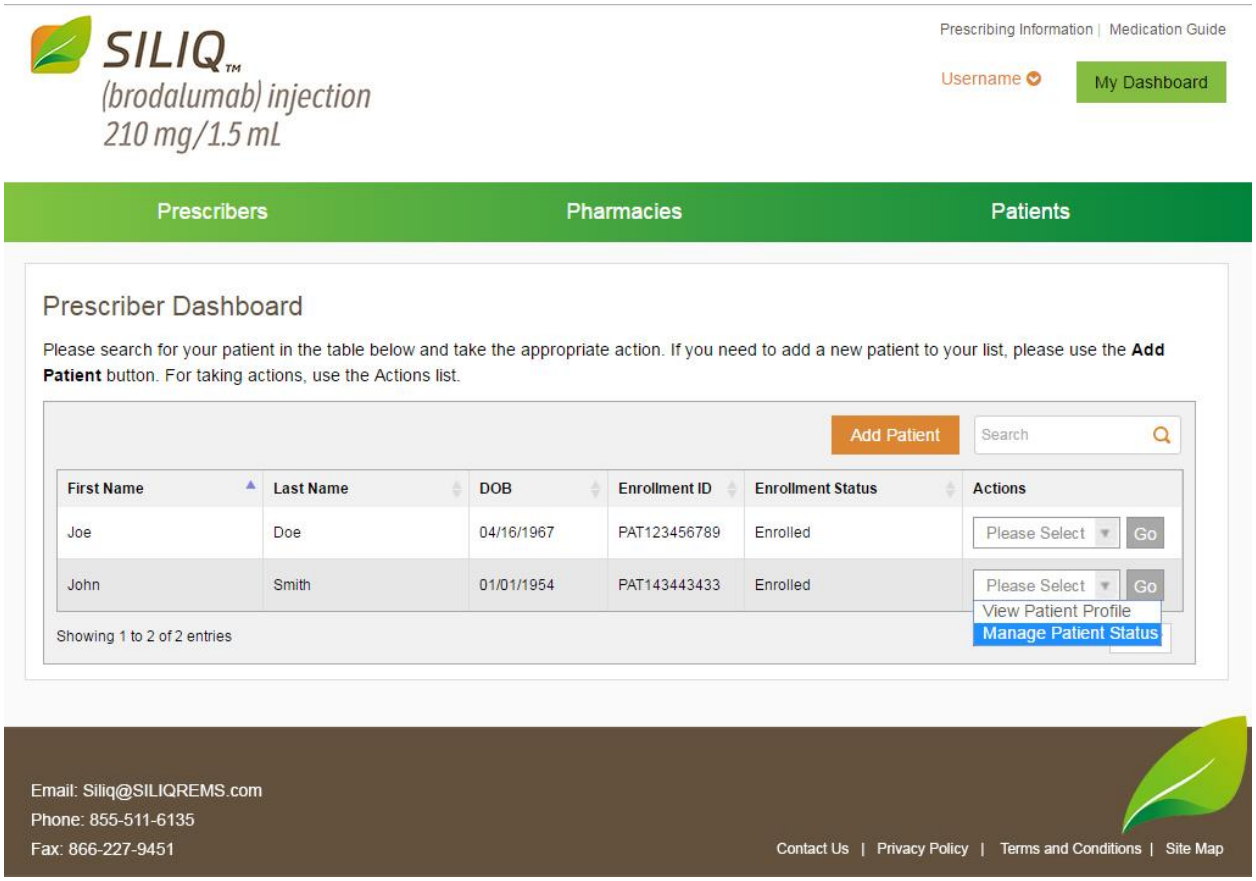


4.3 Patient Enrollment Confirmation Page

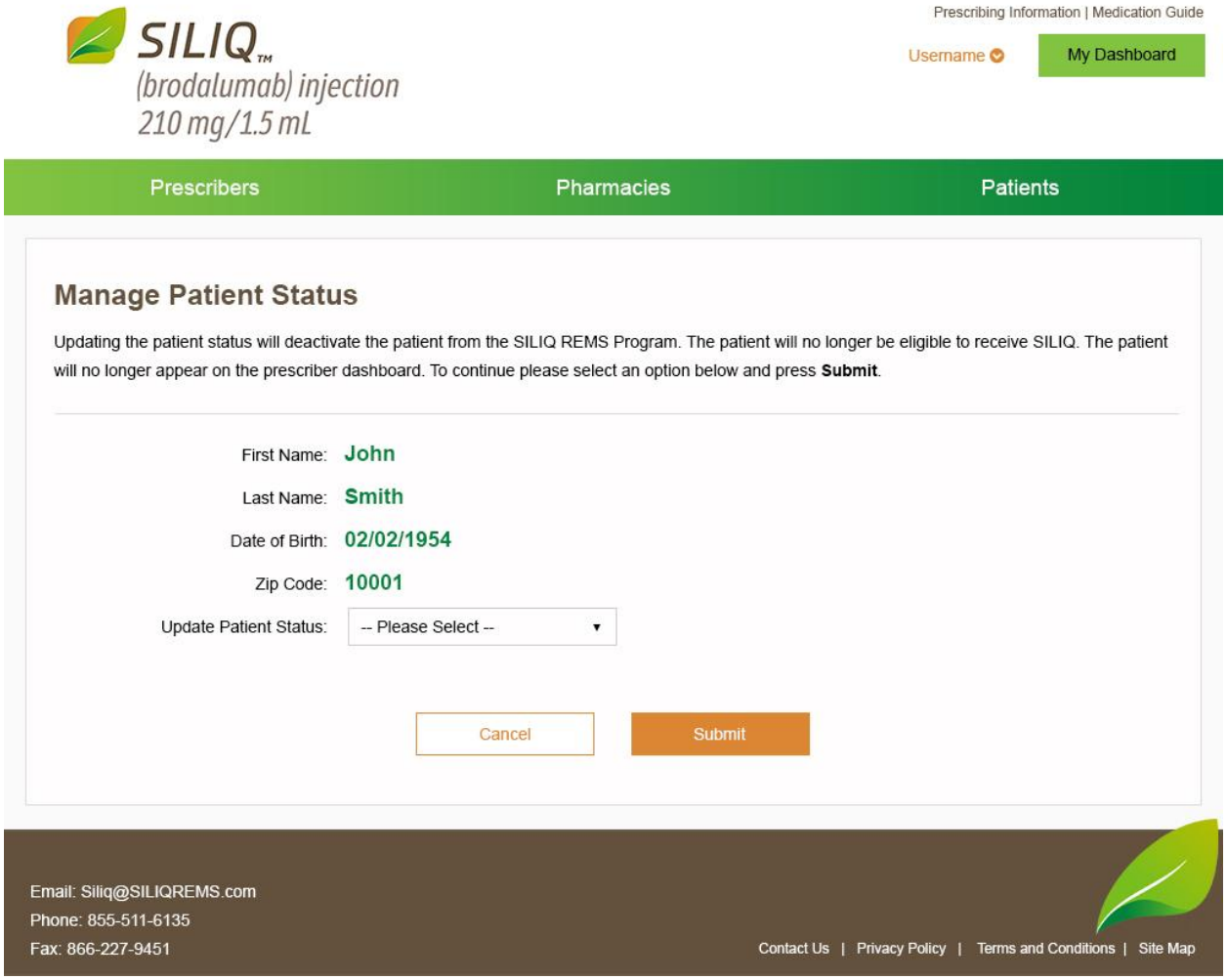


5. Dashboard

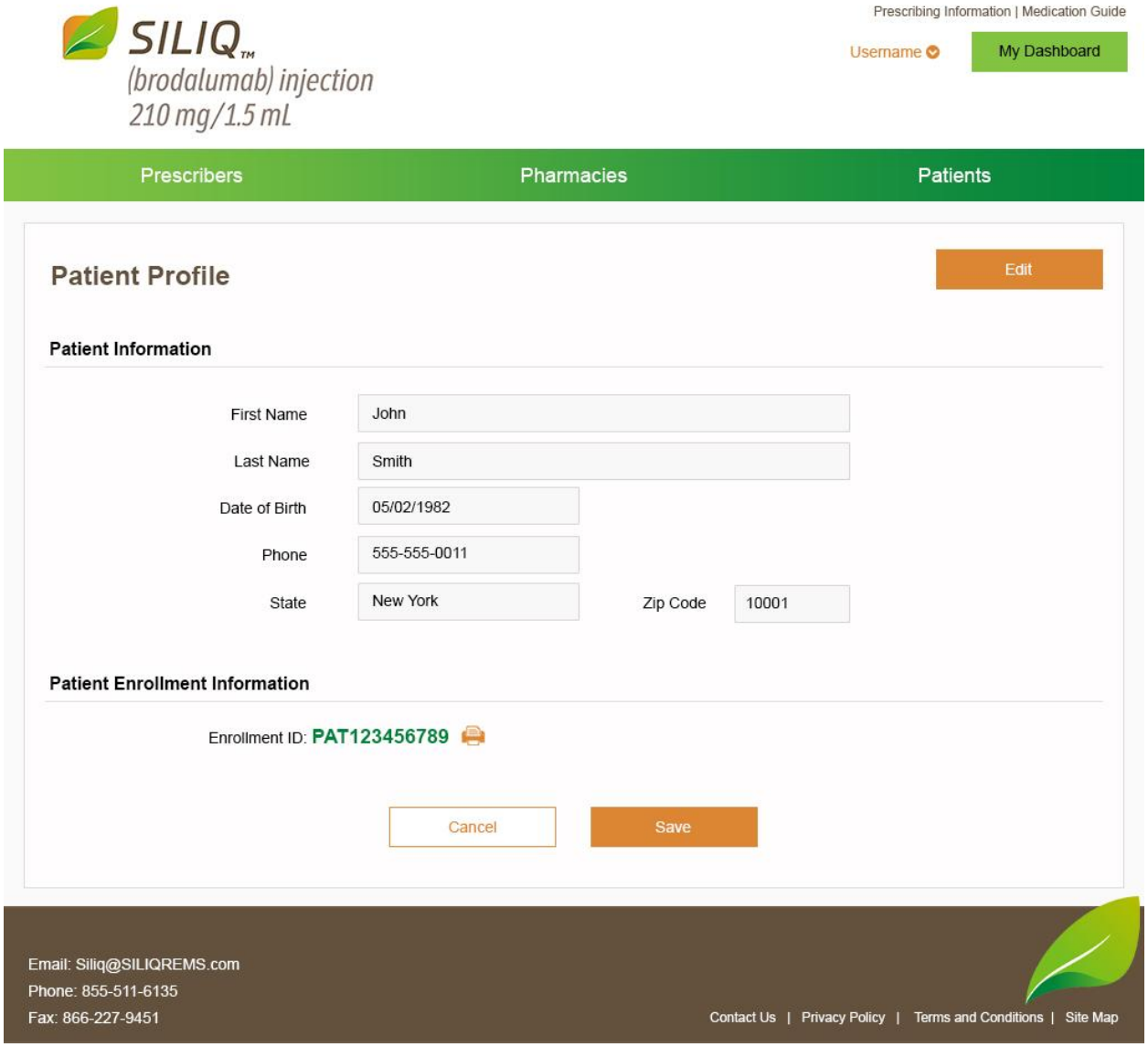
5.1 Prescriber Dashboard



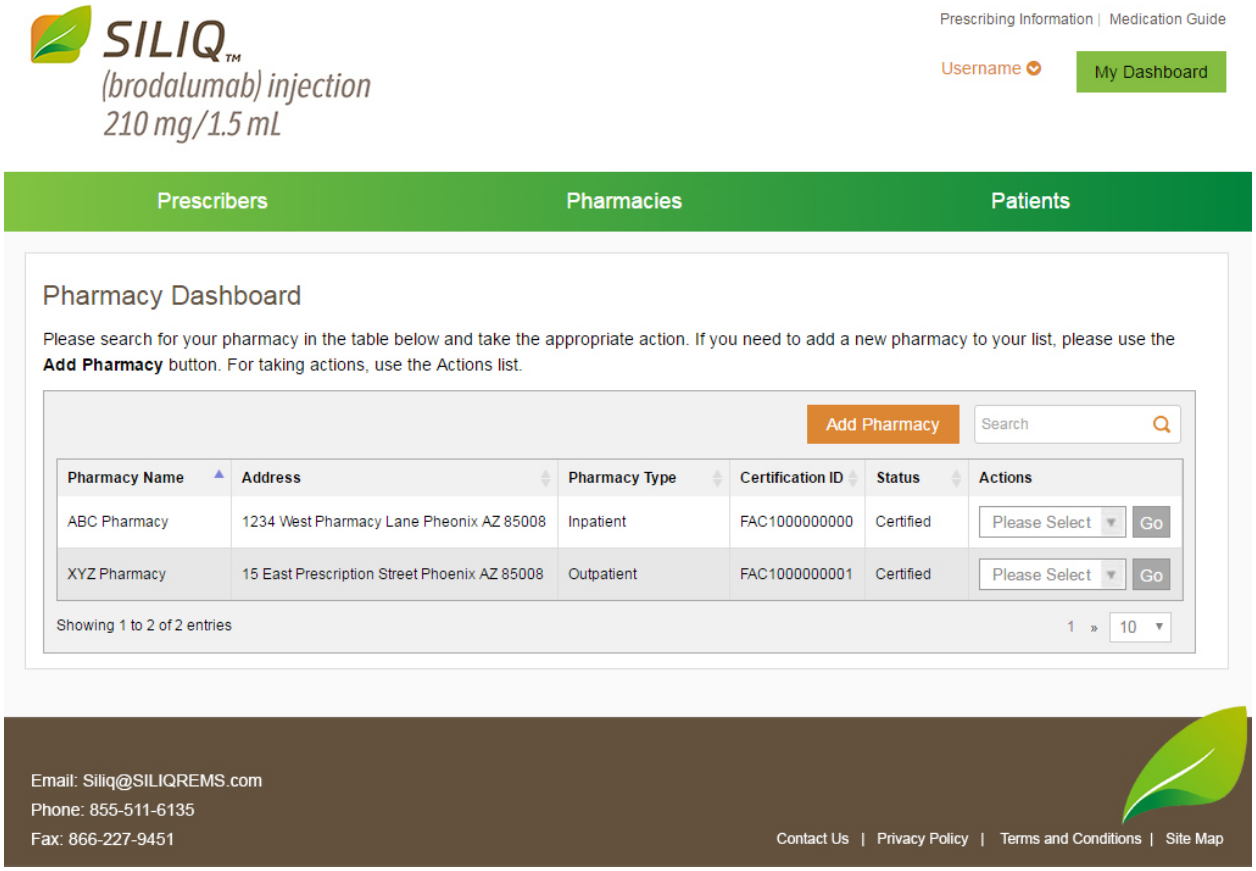
5.2 Manage Patient Status



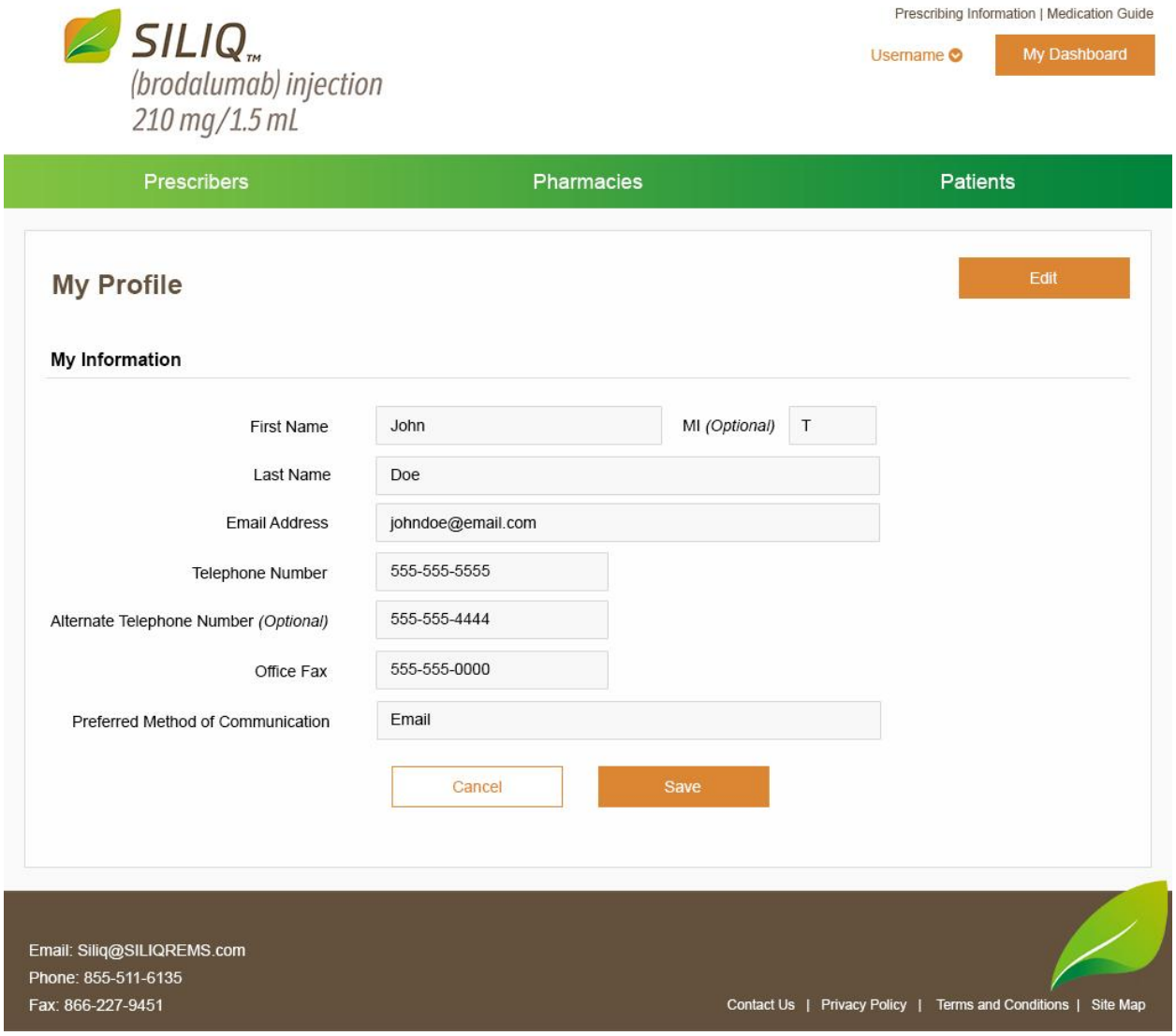
5.3 View Patient Profile



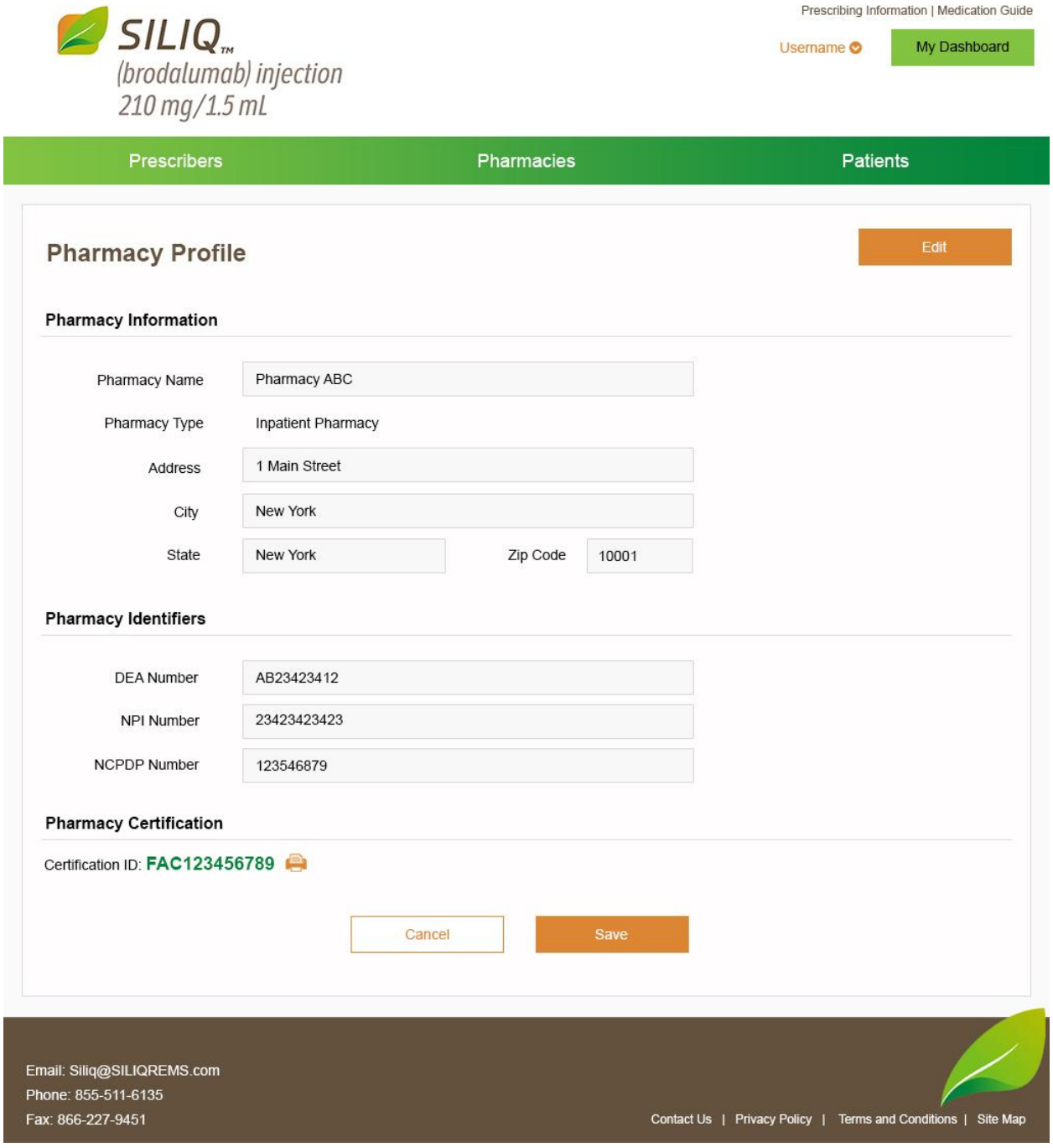
5.4 Pharmacy Dashboard



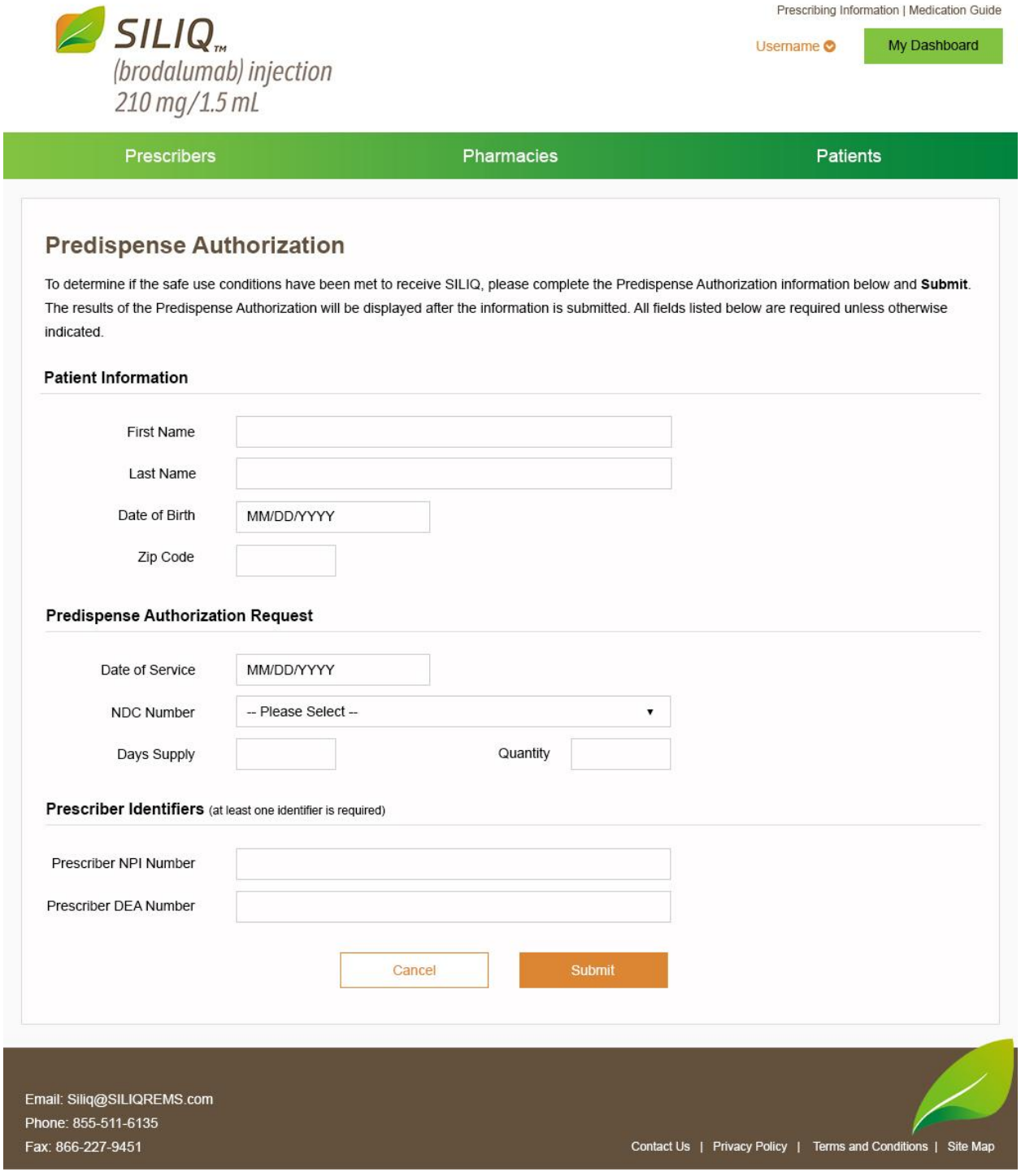
5.5 Edit Authorized Pharmacy Representative Profile



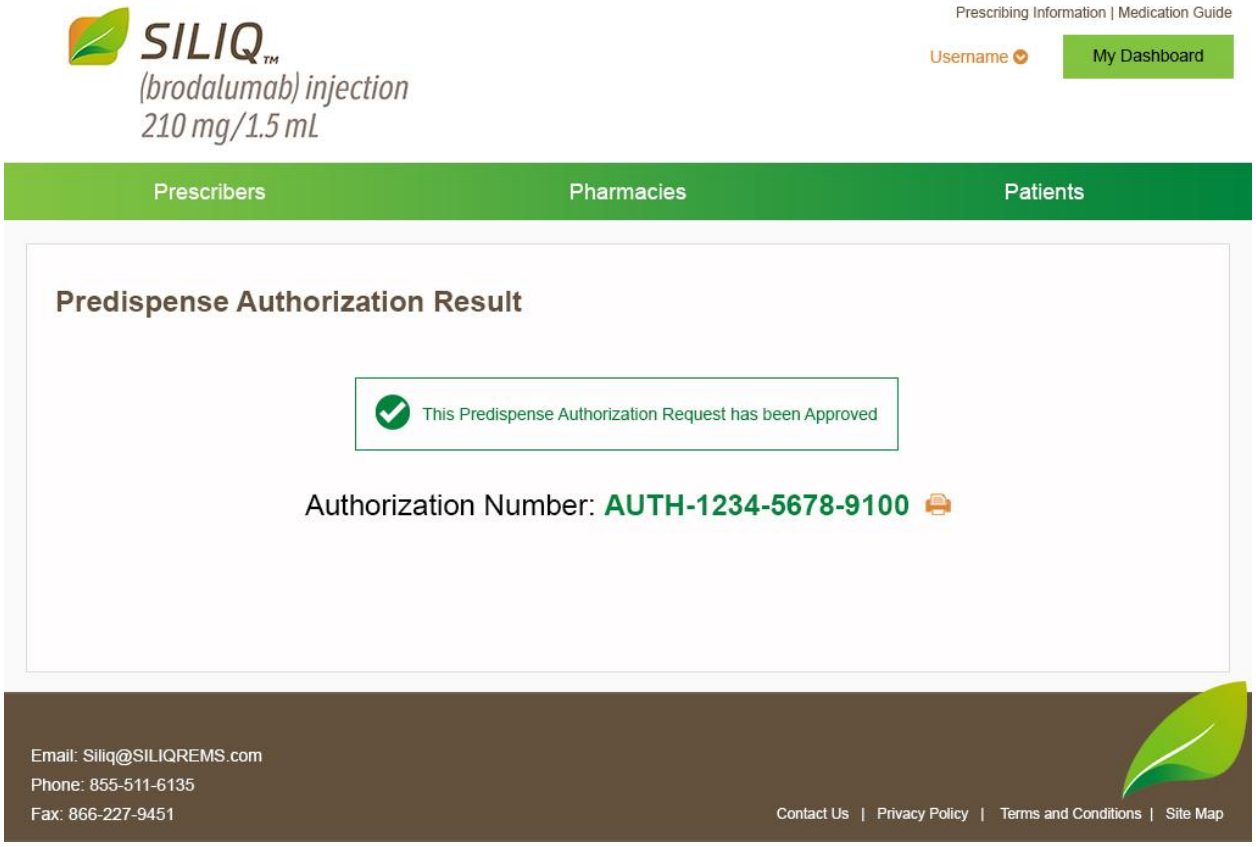
5.6 View Pharmacy Profile



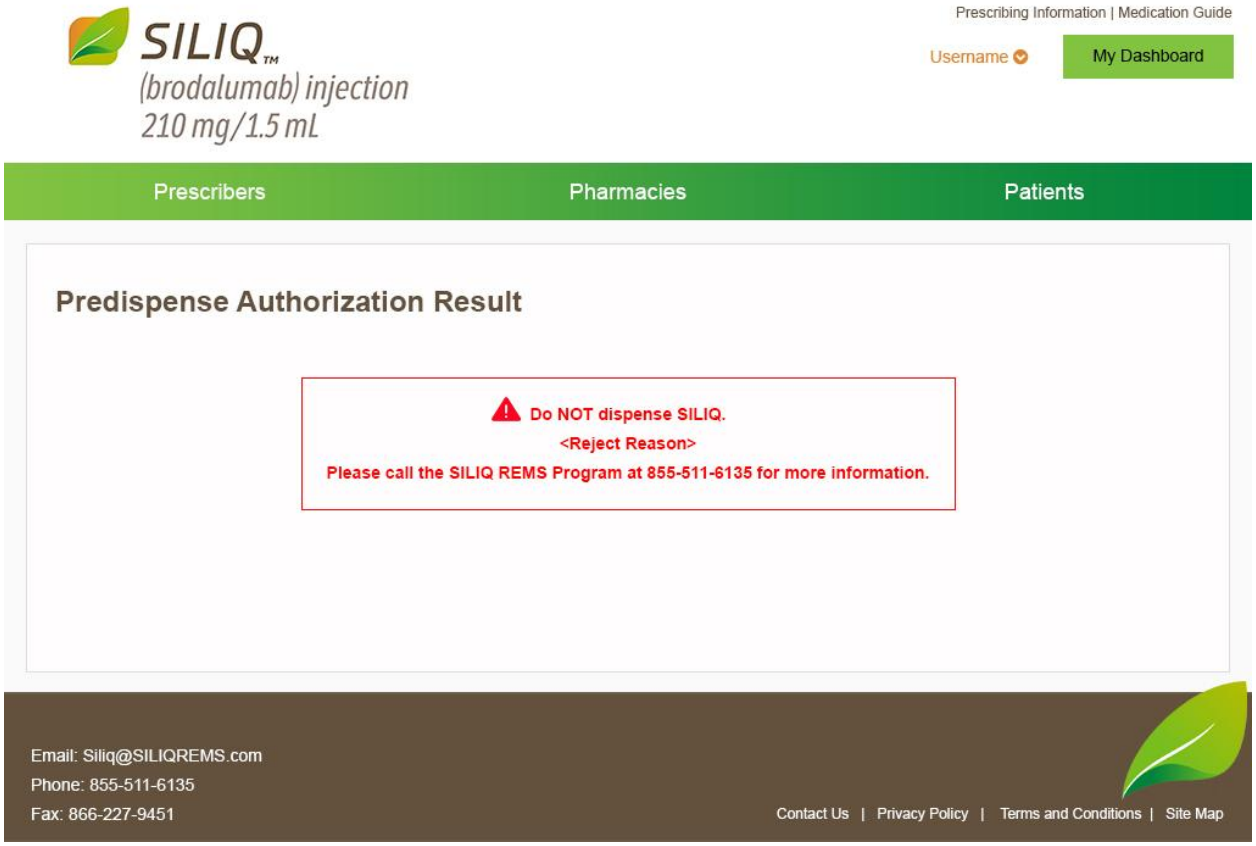
5.7 Predispense Authorization (PDA) Intake



5.8 Predispense Authorization (PDA) Confirmation

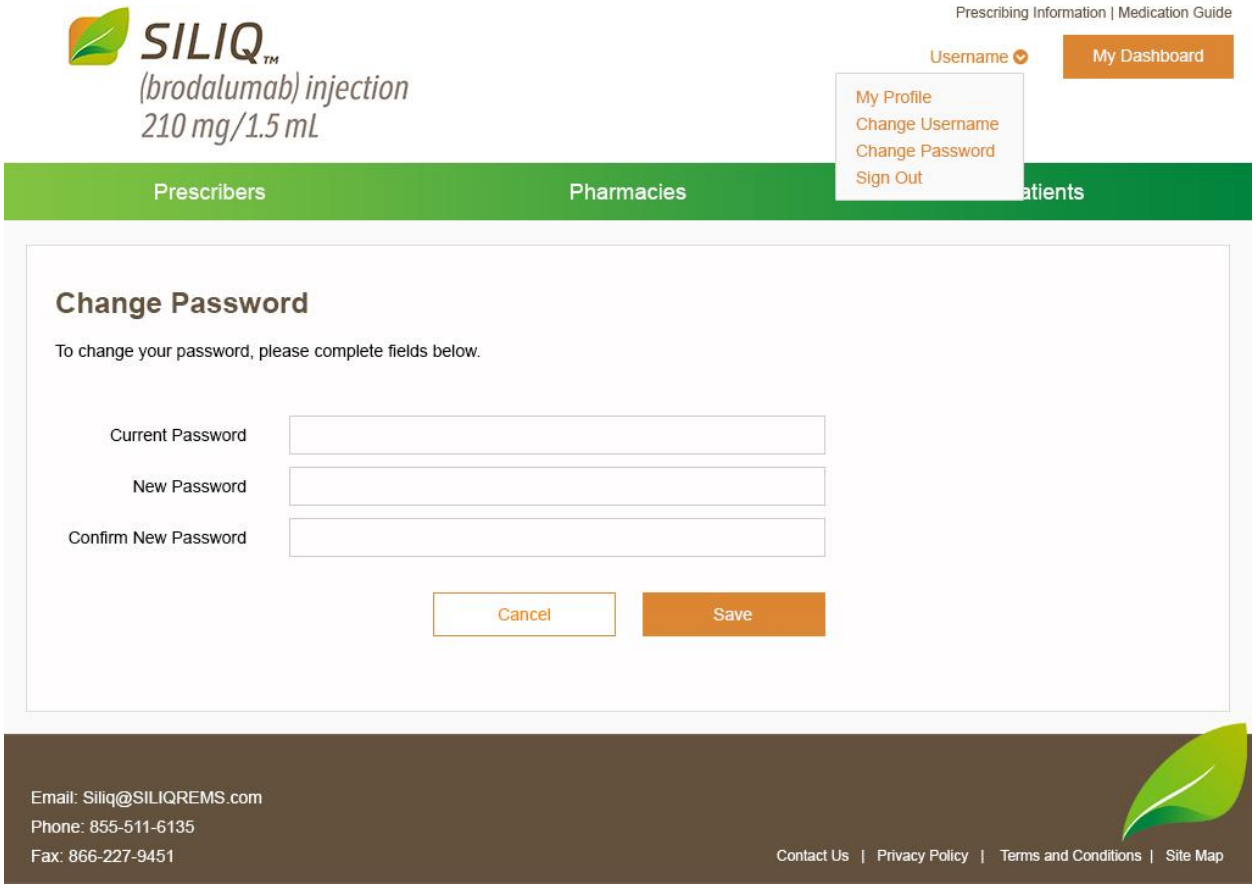


5.9 Predispense Authorization (PDA) Rejection

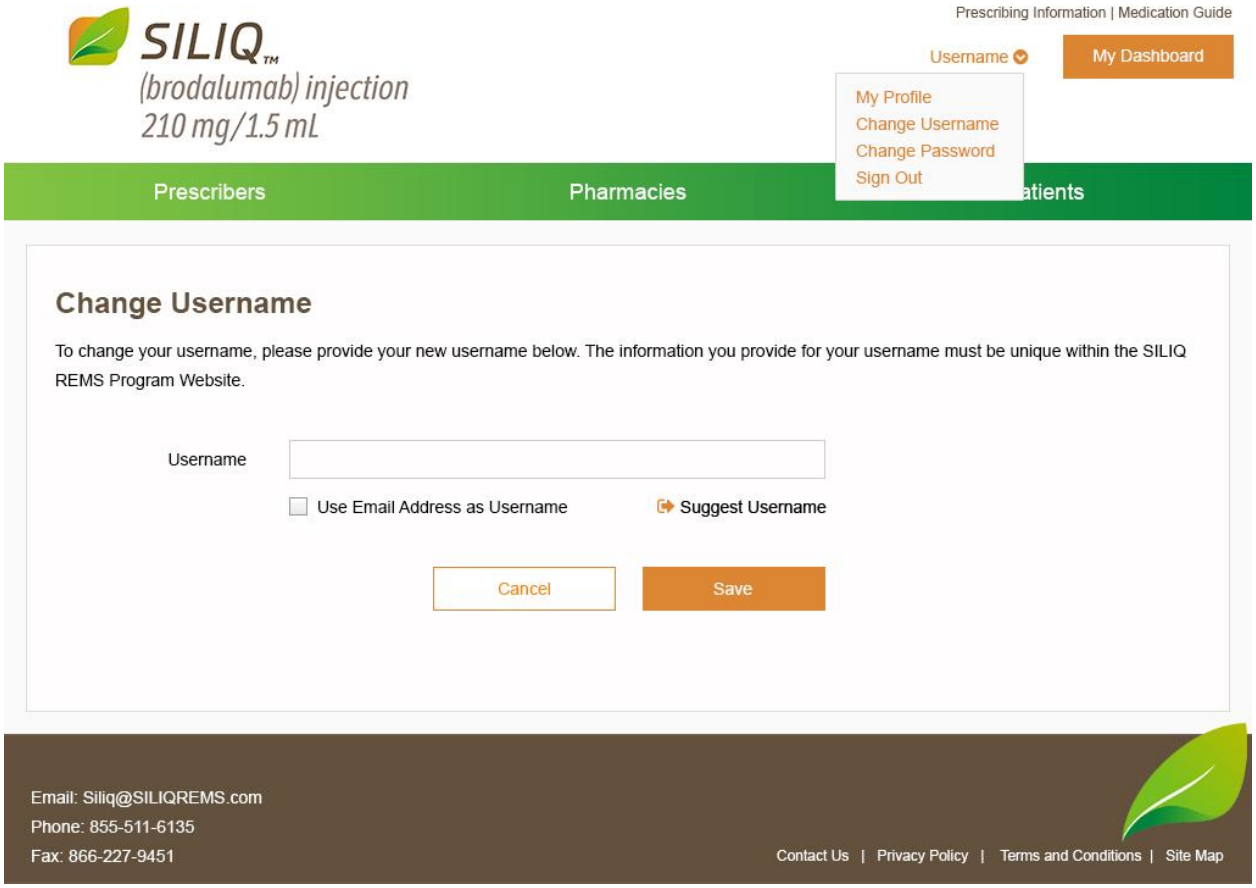


6. Account

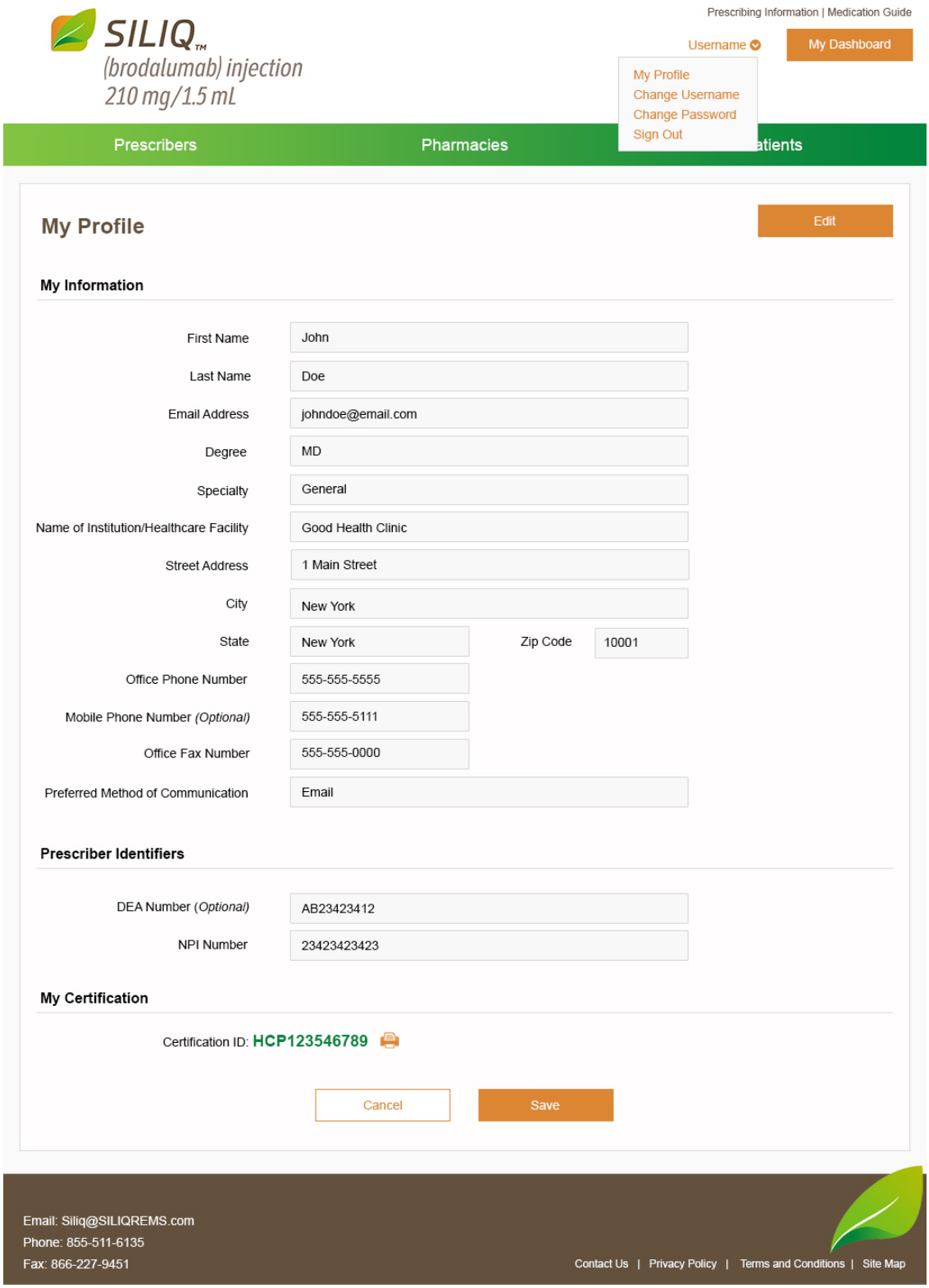
6.1 Change Password



6.2 Change Username



6.3 Edit Prescriber Profile



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

/s/

KENDALL A MARCUS
02/15/2017