

## 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. (2.2)

### DOSAGE FORMS AND STRENGTHS

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

### CONTRAINDICATIONS

- Crohn's disease (4)

- Clinically significant hypersensitivity to brodalumab or to any of the excipients in SILIQ or component of the container (4)

### WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions:** Serious hypersensitivity reactions, including anaphylaxis, may occur. If a serious hypersensitivity reaction occurs, immediately discontinue SILIQ and initiate appropriate therapy. (5.3)
- **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. (5.4)
- **Tuberculosis (TB):** Evaluate patients for TB infection prior to initiating treatment with SILIQ. (5.5)
- **Eczematous Eruptions:** The onset of eczematous eruptions was variable, ranging from days to months after the first dose of SILIQ. Some cases of severe eczematous eruptions resulted in hospitalization. Treatment may need to be discontinued to resolve the eczematous eruption. Some patients with limited psoriasis treatment options were successfully treated for eczema while continuing SILIQ. (5.6)
- **Crohn's Disease:** Crohn's disease occurred during clinical trials. Discontinue SILIQ if patient develops Crohn's disease while taking SILIQ. (5.7)
- **Immunizations:** Avoid using live vaccines concurrently with SILIQ. (5.8)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 1\%$ ) were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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## 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<sup>®</sup> (brodalumab) 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 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)].

### 2.2 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.

### 2.3 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. 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.

### 4 CONTRAINDICATIONS

SILIQ is contraindicated in patients with:

- Crohn's disease because SILIQ may cause worsening of disease [see *Warnings and Precautions (5.7)*].
- Clinically significant hypersensitivity to brodalumab or to any of the excipients in SILIQ or component of the container. Hypersensitivity reactions, including anaphylaxis, have been reported with postmarket use of SILIQ [see *Warnings and Precautions (5.3)*].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Suicidal Ideation and Behavior

Suicidal ideation and behavior, including four 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 Enrollment Form.
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive SILIQ.
- Distributors must be authorized to distribute SILIQ and must only distribute to certified prescribers and pharmacies.

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

### 5.3 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been reported with postmarket use of SILIQ. Some cases required hospitalization. If a serious hypersensitivity reaction occurs, immediately discontinue SILIQ and initiate appropriate therapy.

### 5.4 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.

### 5.5 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.

### 5.6 Eczematous Eruptions

Postmarketing cases of severe eczematous eruptions, including atopic dermatitis-like eruptions, were reported in patients receiving SILIQ. The onset of eczematous eruptions was variable, ranging from days to months after the first dose of SILIQ. Some cases of severe eczematous eruptions resulted in hospitalization. Treatment may need to be discontinued to resolve the eczematous eruption. Some patients with limited psoriasis treatment options were successfully treated for eczema while continuing SILIQ.

### 5.7 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.

### 5.8 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)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- Infections [see Warnings and Precautions (5.4)]
- Crohn's Disease [see Contraindications (4), Warnings and Precautions (5.7)]

## 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 4,558 subjects (3,066 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, 4,464 subjects received at least one dose of SILIQ; 3,755 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 <sup>a</sup> (N=1,496) n (%)	Ustekinumab (N=613) <sup>b</sup> 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)

<sup>a</sup> Subjects receiving 210 mg of SILIQ at Weeks 0, 1, and 2, followed by treatment every 2 weeks during the 12-week period.

<sup>b</sup> 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 4,019 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 4,464 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* (5.4)].

##### *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  $\geq$  Grade 3 ( $< 1,000/\text{mm}^3$ ) 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  $\geq$  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.

### 6.3 Postmarketing Experience

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

*Immune System Disorders:* Hypersensitivity reactions, anaphylaxis, including anaphylactic shock, pruritus, rashes, eczema, urticaria, and dermatitis [see *Contraindications (4)*, *Warnings and Precautions (5.3)*].

*Skin and Subcutaneous Tissue Disorders:* Eczematous eruptions (atopic dermatitis-like eruptions) [see *Warnings and Precautions (5.6)*].

## 7 DRUG INTERACTIONS

### CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF $\alpha$ , 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 postnatal 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 postnatal 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 3,066 plaque psoriasis subjects initially randomized to SILIQ in clinical trials, 192 (6%) were  $\geq 65$  years old and no subjects were  $\geq 75$  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 IgG2 $\kappa$  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. SILIQ is supplied in a single-dose syringe made from type 1 glass with stainless steel 27G x 1/2" 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 ( $\pm$ SD) serum concentration ( $C_{max}$ ) of 13.4 $\pm$ 7.3 mcg/mL by approximately 3 days post-dose. The mean ( $\pm$ SD) area-under-the-concentration-time curve (AUC) of brodalumab was 111 $\pm$ 64 mcg $\cdot$ day/mL.

Following multiple subcutaneous doses of 210 mg every 2 weeks, steady-state was achieved by Week 4. The mean ( $\pm$ SD)  $C_{\max}$  was 20.6 $\pm$ 14.6 mcg/mL and the mean ( $\pm$ SD) AUC over the 2-week dosing interval was 227 $\pm$ 167 mcg $\cdot$ 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 ( $\pm$ SD) apparent volume of distribution ( $V_z/F$ ) of brodalumab was 8.9 $\pm$ 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 ( $\pm$ SD) apparent total clearance ( $CL/F$ ) was 3.0 $\pm$ 3.5 L/day. The clearance of brodalumab increased with decreasing doses due to nonlinear elimination.

#### Dose Linearity

Brodalumab exhibited nonlinear 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* (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 6 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  $\geq 12$ , a static Physician's Global Assessment (sPGA) score  $\geq 3$  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<sup>a</sup>)**

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 <sup>b</sup> 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) <sup>b</sup>	65 (22)	2 (1)	229 (37) <sup>b</sup>	58 (19)	1 (<1)
sPGA success clear (0) or almost clear (1) <sup>b</sup>	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)

<sup>a</sup>NRI = non-responder imputation  
<sup>b</sup>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**

### How Supplied

SILIQ<sup>®</sup> (brodalumab) injection is available in a single-dose prefilled syringe containing a sterile, preservative-free clear to slightly opalescent, colorless to slightly yellow solution.

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

### 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.

### Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [see *Warnings and Precautions* (5.3)].

### 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* (5.4)].

### Eczematous Eruptions

Inform patients that skin reactions resembling eczema may occur with the use of SILIQ. Instruct patients to seek medical advice if they develop signs or symptoms of eczema [*see Warnings and Precautions (5.6)*].

### Crohn's Disease

Instruct patients to seek medical advice if they develop signs and symptoms of Crohn's disease [*see Warnings and Precautions (5.7)*].

### Immunization

Instruct patients to inform their healthcare provider that they are taking SILIQ prior to a potential vaccination [*see Warnings and Precautions (5.8)*].

### 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 (2.2) and Instructions for Use*].

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

### **Distributed by:**

Bausch Health US, LLC  
Bridgewater, NJ 08807 USA

### **Manufactured by:**

Bausch Health Ireland, Limited  
Dublin, Leinster, Ireland 24

U.S. License Number: 2365

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## MEDICATION GUIDE

Siliq® (sil-eeek)

(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 and 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 and behavior. Get medical help right away or call the National Suicide and Crisis Lifeline at 988, if you or your caregiver notice in you any of the following symptoms:
  - new or worsening depression or anxiety
  - thoughts of suicide, dying, or hurting yourself
  - changes in behavior or mood
  - acting on dangerous impulses
  - attempt to commit suicide

**Because of your risk of suicidal thoughts and behavior during your treatment with SILIQ, SILIQ is available only through a restricted distribution program called the SILIQ Risk Evaluation and Mitigation Strategy (REMS).** Before you can receive SILIQ:

- Your healthcare provider must:
  - enroll in the SILIQ REMS
  - give you a **SILIQ Patient Wallet Card** which explains the symptoms that you should get medical help for right away
- You must:
  - sign a **Patient Enrollment Form**
  - carry the **Patient Wallet Card** with you at all times during treatment with SILIQ

SILIQ is only available through pharmacies that participate in the SILIQ REMS. Your healthcare provider can give you information about how to find a participating pharmacy. For more information, go to [www.SILIQREMS.com](http://www.SILIQREMS.com) or call 1-855-511-6135.

- **Serious allergic reactions.** Get medical help right away if you get any of the following signs or symptoms of a serious allergic reaction:
  - swelling of the face, lips, or tongue
  - trouble breathing or swallowing
  - itching
  - dizziness or feel faint
  - rash, hives, or redness all over your body
  - chest pain or tightness
- **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 develop any symptoms of an infection, including:

  - fever, sweats, or chills
  - muscle aches
  - cough
  - shortness of breath
  - sore throat or difficulty swallowing
  - warm, red, or painful skin or sores on your body

- diarrhea or stomach pain
- 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.
- are allergic to brodalumab or any of the ingredients in SILIQ. See the end of this Medication Guide for a list of ingredients in SILIQ.

### **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.
- 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 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?”**
- **Severe skin reactions that look like eczema** can happen during treatment with SILIQ from days to months after your first dose and can sometimes lead to hospitalization. Your healthcare provider may temporarily stop treatment with SILIQ if you develop severe skin reactions. Tell your healthcare provider if you have any of the following signs or symptoms:
  - redness or rash
  - itching
  - small bumps or patches
  - your skin is dry or feels like leather
  - blisters on the hands or feet that ooze or become crusty
  - skin peeling
- **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.

These are not all the possible side effects of SILIQ.

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

### **How should I store SILIQ?**

- 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) 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.
- **Do not** shake.
- Keep SILIQ prefilled syringe in the original carton to protect from light and physical damage.

**Keep SILIQ and all medicines out of the reach of children.**

**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.

**What are the ingredients in SILIQ?**

**Active ingredient:** brodalumab

**Inactive ingredients:** glutamate, polysorbate 20, proline, and Water for Injection.

**Distributed by:** Bausch Health US, LLC

Bridgewater, NJ 08807 USA

**Manufactured by:** Bausch Health Ireland, Limited

Dublin, Leinster, Ireland 24

U.S. License Number: 2365

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For more information, go to [www.SILIQ.com](http://www.SILIQ.com) or call Bausch Health US, LLC at 1-800-321-4576.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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