CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
2Q17 April – May

BRAND NAME
Siliq™

GENERIC NAME
Brodalumab

MANUFACTURER
Valeant Pharmaceuticals

DATE OF APPROVAL
February 15, 2017

PRODUCT LAUNCH DATE
Second half of the year (Q3 or Q4 2017)

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

FDA APPROVED INDICATION(S)
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.

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY
The safety and efficacy of brodalumab were investigated in three phase 3 trials. One was a multicenter, randomized, double-blind, placebo-controlled trial. The other two were multicenter,

randomized, double-blind, placebo-controlled and active comparator-controlled, parallel-group trials. Ustekinumab was used in the active comparator arm. The three trials enrolled a total of 4373 patients and measured the change from baseline to week 12. Additionally, each study included a 40 week maintenance (withdrawal/retreatment) phase.

The primary endpoints were Psoriasis Area and Severity Index 75 (PASI 75) (≥75% reduction in PASI score) and a static Physician's Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) and a 2 point improvement from baseline. Secondary endpoints included proportion of subjects who achieved a sPGA score of 0, PASI 100, and 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. In the 2 trials that included ustekinumab, a PASI 100 from baseline at week 12 was a primary endpoint.

In trial 1, patients received placebo or subcutaneous brodalumab 140 mg or 210 mg at weeks 0, 1, and 2 followed by injections every 2 weeks for 12 weeks. The results discussion here is focused on the dose that was ultimately FDA approved, brodalumab 210 mg. The endpoint of PASI 75 was 83% (95% CI 78-88) for brodalumab and 3% (95% CI 1-6) for placebo ($p<0.001$). The proportion of patients achieving a sPGA score of 0 or 1 was 76% (95% CI 70-81) for brodalumab and 1% (95% CI 0-4) for placebo ($p<0.001$).

At week 12, patients receiving brodalumab with a sPGA score of 0 or 1 were re-randomized to receive either their induction doses of brodalumab or placebo; those with a sPGA score of ≥2 or who were originally randomized to placebo received brodalumab 210 mg every 2 weeks. Beginning at week 16, re-randomized patients who experienced return of the disease (sPGA score of ≥3) received their induction dose of brodalumab. In addition, patients with inadequate response to at least 12 weeks of retreatment (sPGA score of 2 over a 4 week period or sPGA score of ≥3) received open-label brodalumab 210 mg every 2 weeks. At the end of the 52 week period, sPGA success was 83% for brodalumab and 0% for placebo ($p<0.001$). Of the patients with return of disease after week 16, 97% were able to recapture sPGA success after 12 weeks of retreatment. Further, the proportion of patients achieving PASI 100 was 68% for brodalumab and 0% for placebo ($p<0.001$). The percentages of patients with PASI 90 and PASI 100 were maintained through week 52 among responders at week 12 who were re-randomized to their induction dose of brodalumab.

In trials 2 and 3, patients received placebo, subcutaneous brodalumab 140 mg or 210 mg at weeks 0, 1, and 2 followed by injections every 2 weeks, or subcutaneous ustekinumab based on weight (45 mg if ≤45 kg and 90 mg if >100 kg) at weeks 0, 4, and 16 followed by the same dose every 12 weeks. The results discussion here is focused on the dose that was ultimately FDA approved, brodalumab 210 mg. The proportion of patients achieving the following primary outcomes were:

- PASI 75:
    - Trial 2: 86% (95% CI 83-89) for brodalumab vs. 8% (95% CI 5-12) for placebo

  - Trial 3: 85% (95% CI 82-88) for brodalumab vs. 6% (95% CI 4-9) for placebo
- sPGA score of 0 or 1:
  - Trial 2: 79% (95% CI 75-82) for brodalumab vs. 4% (95% CI 2-7) for placebo
  - Trial 3: 80% (95% CI 76-83) for brodalumab vs. 4% (95% CI 2-7) for placebo
- PASI 100:
  - Trial 2: 44% (95% CI 41-49) for brodalumab vs. 22% (95% CI 17-27) for ustekinumab
  - Trial 3: 37% (95% CI 33-41) for brodalumab and 19% for ustekinumab (95% CI 14-23)

These outcomes were all statistically significant ($p<0.001$).

At week 12, patients receiving brodalumab underwent re-randomization to brodalumab 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks, or 140 mg every 8 weeks. Patients originally randomized to receive placebo were switched to brodalumab 210 mg every 2 weeks, and those receiving ustekinumab continued their ustekinumab dose. At week 16, patients who were randomized to receive brodalumab who had a sPGA score of 2 over a 4 week period or sPGA score of ≥3 received rescue treatment with 210 mg of brodalumab every 2 weeks. Those receiving ustekinumab with an inadequate response also received 210 mg of brodalumab every 2 weeks. For patients who did not respond to the rescue treatment, the study drug was then discontinued. In trial 2, 18% in the ustekinumab group received rescue therapy with brodalumab while 22% in trial 3 received rescue therapy. Approximately 40% of those patients had a PASI 100 at week 52, and the majority reached sPGA score of 0 or 1 and PASI 75 at week 52. In addition, most patients who switched to brodalumab from placebo had a sPGA score of 0 or 1 and PASI 75 at week 52, with the majority achieving PASI 100.

CONTRAINDICATIONS
Siliq is contraindicated in patients with Crohn's disease.

BLACK BOX WARNINGS
Siliq has a black box warning for suicidal ideation and behavior and it is only available through a restricted program called the Siliq REMS program. A causal association between treatment with Siliq and increased risk of suicidal ideation and behavior has not been established. However, because of the observed suicidal ideation and behavior in subjects treated with Siliq, consider discontinuing therapy if an adequate response to Siliq has not been achieved within 12 to 16 weeks.

DRUG INTERACTIONS
Avoid the use of live vaccines in patients treated with Siliq.

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. Therefore, consider monitoring for

effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine), and consider dosage modification of the CYP450 substrate.

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

DOSAGE AND ADMINISTRATION
Administer 210 mg of Siliq by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.

PRODUCT AVAILABILITY
Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe.

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Etanercept (Enbrel)	Subcutaneous injection of 50 mg twice weekly for 3 months, then 50 mg once weekly	A tumor necrosis factor (TNF) blocker indicated in those 4 years or older for plaque psoriasis
Infliximab (Remicade)	Intravenous infusion of 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	A TNF blocker
Adalimumab (Humira)	Subcutaneous injection of 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose	A TNF blocker
Ustekinumab (Stelara)	Subcutaneous injection of 45 mg to 90 mg initially and 4 weeks later, then 45 mg to 90 mg every 12 weeks	A human interleukin-12 and -23 antagonist
Secukinumab (Cosentyx)	Subcutaneous injection of 300 mg at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks	A human interleukin-17A antagonist
Ixekizumab (Taltz)	Subcutaneous injection of 160 mg (two 80 mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	A human interleukin-17A antagonist

Boldface indicates generic availability

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Utilization Management Recommendation
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) Siliq is the only biologic agent for the treatment of plaque psoriasis with a black box warning for suicidal ideation and behavior. ii) Siliq is FDA approved as a second line agent after failure or inadequate response to other systemic therapies. iii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
• CPAC score: 66 vs. Stelara (ustekinumab) - Modest benefits over current therapies • CPAC score: 54 vs. Taltz (ixekizumab) - Equal therapeutic outcomes anticipated • Equal therapeutic outcomes are anticipated for Taltz and Siliq; therefore, it would be appropriate to provide equal access to both Taltz and Siliq. • It would not be clinically appropriate to require a trial of Siliq prior to Taltz due to the black box warning for suicidal ideation associated with Siliq. • Modest therapeutic outcomes are anticipated for Siliq over Stelara for the treatment of plaque psoriasis; therefore, it would not be clinically appropriate to require a trial of Stelara prior to Siliq.