CENTENE PHARMACY AND THERAPEUTICS
NEW DRUG REVIEW
3Q17 July – August

BRAND NAME
Dupixent®

GENERIC NAME
dupilumab

MANUFACTURER
Regeneron

DATE OF APPROVAL
March 28, 2017

PRODUCT LAUNCH DATE
First week of April 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)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)
Dupixent is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.

OFF-LABEL USES
Not applicable

CLINICAL EFFICACY[1, 2]

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Three randomized, double-blind, placebo-controlled trials (LIBERTY AD: SOLO 1, SOLO 2, CHRONOS) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score $\geq$3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score $\geq$16 on a scale of 0 to 72, and a minimum body surface area involvement of $\geq$10%.

At baseline, 59% of subjects were male, 67% were white, 52% had a baseline IGA score of 3 (moderate AD), and 48% had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33, and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the Dupixent group received subcutaneous injections of Dupixent 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (SOLO 1 and 2), subjects received Dupixent or placebo for 16 weeks. In the concomitant therapy trial (CHRONOS), subjects received Dupixent or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous, and genital areas for 52 weeks.

All three trials assessed the same primary endpoint, the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in the peak pruritus NRS from baseline to Week 16.

The results from SOLO 1 showed that the primary outcome occurred in 85 patients (38%) who received Dupixent every other week and in 83 (37%) who received Dupixent weekly, as compared with 23 (10%) who received placebo ($P<0.001$ for both comparisons). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received Dupixent every other week and in 87 (36%) who received Dupixent weekly, as compared with 20 (8%) who received placebo ($P<0.001$ for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of Dupixent than in patients who received placebo ($P<0.001$ for all comparisons). Dupixent was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. Injection-site reactions and conjunctivitis were more frequent in the Dupixent groups than in the placebo groups.

Four patients from Dupixent active arm, compared to three patients from the placebo arm, withdrew from the studies due to lack of efficacy.

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The results from CHRONOS showed that at 52 weeks, 36% (N=32/89) of patients taking Dupixent plus topical corticosteroids showed response, whereas only 13% (N=34/264) patients taking placebo and topical corticosteroid were categorized as responders.

CONTRAINDICATIONS
Contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients

BLACK BOX WARNINGS
Not applicable

DRUG INTERACTIONS
- Avoid use of live vaccines.
- Monitor for potential interaction with CYP450 substrates.

ADVERSE REACTIONS
- Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.
- Less common but more serious adverse reactions included:
  - Generalized urticarial and serum sickness/serum sickness-like reactions (<1%)
  - Keratitis (<1%)
  - Greater mean initial increase from baseline in eosinophil count (<1%)
  - Auto-antibody formation, leading to lower serum dupilumab concentrations (7-8%)

DOSAGE AND ADMINISTRATION
The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites) via subcutaneous injection, followed by 300 mg given every other week.

PRODUCT AVAILABILITY
Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with or without needle shield

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Very High Potency Topical Corticosteroids		
augmented betamethasone 0.05% (Diprolene® AF) cream, ointment, gel, lotion	Apply topically to the affected area(s) BID	
clobetasol propionate 0.05% (Temovate®) cream, ointment, gel,		

solution		
diflorasone diacetate 0.05% (Maxiflor®, Psorcon E®) cream, ointment		
halobetasol propionate 0.05% (Ultravate®) cream, ointment		
High Potency Topical Corticosteroids		
augmented betamethasone 0.05% (Diprolene® AF) cream, ointment, gel, lotion	Apply topically to the affected area(s) BID	
diflorasone 0.05% (Florone®, Florone E®, Maxiflor®, Psorcon E®) cream		
fluocinonide acetonide 0.05% (Lidex®, Lidex E®) cream, ointment, gel, solution		
triamcinolone acetonide 0.5% (Aristocort®, Kenalog®) cream, ointment		
Medium Potency Topical Corticosteroids		
desoximetasone 0.05% (Topicort ®) cream, ointment, gel	Apply topically to the affected area(s) BID	
fluocinolone acetonide 0.025% (Synalar®) cream, ointment		
mometasone 0.1% (Elocon®) cream, ointment, lotion		
triamcinolone acetonide 0.025%, 0.1% (Aristocort®, Kenalog®) cream, ointment		
Low Potency Topical Corticosteroids		
alclometasone 0.05% (Aclovate®) cream, ointment	Apply topically to the affected area(s) BID	
desonide 0.05% (Desowen®) cream, ointment, lotion		
fluocinolone acetonide 0.01% (Synalar®) solution		
hydrocortisone 2.5% (Hytone®) cream, ointment		
Other Class of Agents		
Elidel® (pimecrolimus) 1% cream	Apply topically to the affected area(s) BID	If no improvement within 6 weeks, patients should be re-examined to confirm diagnosis.
Protopic® (tacrolimus) 0.03% and 0.1%	Apply topically to the	If no improvement within 6

ointment	affected area(s) BID	weeks, patients should be re-examined to confirm diagnosis.
Eucrisa™ (crisaborole) 2% ointment	Apply topically to the affected area(s) BID	
cyclosporine	3-6 mg/kg/day orally BID	Off-label
azathioprine	1-3 mg/kg/day orally once daily	Off-label
methotrexate	7.5-25 mg/wk orally once weekly	Off-label
mycophenolate mofetil	1-1.5 orally BID	Off-label
systemic corticosteroids (e.g., prednisone, prednisolone, triamcinolone)	Oral, intramuscular, or parenteral; dose varies	

Boldface indicates generic availability

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):
  - i) To prevent inappropriate use of medications that have a higher potential to cause patient harm and lead to increased medical utilization compared to therapeutic alternatives.
    - (1) Opportunity exists to obtain clinically significant medical or laboratory information necessary to determine appropriate use of the medication.
      - (a) To ensure that patients have moderate-to-severe atopic dermatitis and the disease is not adequately controlled with topical prescription therapies or those therapies are not advisable.
  - ii) 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[3]

- CPAC score: 59 vs. systemic cyclosporine (off-label) - Equal therapeutic outcomes are anticipated
- Equal therapeutic outcomes are anticipated for Dupixent and cyclosporine; therefore it would be appropriate to provide equal access to both or to require a trial of one before the other.
  - ➢ It would be clinically appropriate to require a trial of one of the following systemic agents

prior to initiation of Dupixent: corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, or cyclosporine.

- It would be clinically appropriate to require a trial of topical corticosteroids, topical calcinuerin inhibitors, and Eucrisa prior to initiation of Dupixent.
  - ➢ It would be clinically appropriate to require up to 4 different agents for redirection.
- It would be clinically appropriate to require a baseline Investigator's global assessment (IGA) score or Eczema Area and Severity Index (EASI) score > 16 points prior to initiation of Dupixent as well as a reduction in IGA or EASI score for documentation of positive response to therapy for continuation of Dupixent.

REFERENCES

[1] Dupixent Prescribing Information. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; March 2017. Available at www.dupixent.com. Accessed March 28, 2017.
[2] Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. New England Journal of Medicine. 2016; 375: 2335-48.
[3] Eichenfield F, Tom WL, Chamlin SL et al. Guidelines of Care for the Management of Atopic Dematitis. J Am Acad Dermatol. 2014 February; 70(2): 338–351