PDL DRUG REVIEW

Proprietary Name: Dupixent®
Common Name: dupilumab
PDL Category: Atopic Dermatitis

Comparable Products	Preferred Drug List Status
Elidel	Non-Preferred with Conditions
Protopic	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Dupilumab, the active ingredient of Dupixent®, is an interleukin-4 receptor alpha antagonist produced by recombinant DNA technology in Chinese Hamster Ovary culture. It is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4Rα subunit and inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling. Blocking IL-4Rα with Dupixent® inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE.

Indications: 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. It can be used with or without topical corticosteroids.

There is no pregnancy category for this product; however, the risk summary indicates that there are no data on use in pregnant women to inform a drug-associated risk. Human IgG antibodies are known to cross the placental barrier, thus Dupixent® may be transmitted from the mother to the developing fetus. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Solution for injection: 300mg/2ml in a single-dose pre-filled syringe. Refrigerate but may be kept at room temperature for a maximum of 14 days.

Recommended Dosage: Remove from refrigeration before injection and allow to reach room temperature (45 minutes). Administer as a subcutaneous (SC) injection into the thigh or abdomen, with an initial dose of 600mg (two 300mg injections administered at different injection sites), followed by 300mg QOW. The injection site should be rotated with each injection. While treatment may be used with or without topical corticosteroids, topical calcineurin inhibitors may be used but should be reserved for problem areas only, such as the face, neck, intertriginous, and genital areas. Treatment may be self-administered after training in SC injection technique.

Studies were not performed to assess the effect of hepatic or renal impairment on the pharmacokinetics of Dupixent®.

Drug Interactions: Avoid live vaccines if treated with Dupixent®. Upon starting or discontinuing treatment in patients 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 dose medication of the CYP450 substrate.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Dupixent®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included injection site reactions (5%), conjunctivitis (8%), blepharitis (0%), oral herpes (2%), keratitis (<1%), eye pruritus (<1%), other herpes simplex virus infection (1%), and dry eye (<1%). Hypersensitivity reactions were reported in less than 1% of subjects treated with Dupixent® in clinical trials.

Due to reports of conjunctivitis and keratitis in clinical trials, it is recommended to advise patients to report new onset or worsening eye symptoms.

The safety and efficacy of Dupixent® have not been established in the treatment of asthma. Patients with comorbid asthma should be advised not to adjust or stop asthma medications without consulting healthcare provider. In addition, patients with known helminth infections were excluded from clinical trials with Dupixent®.

Contraindications: Hypersensitivity to dupilumab or any component of the compound

Manufacturer: Regeneron, Marketed by Sanofi-Aventis and Regeneron

Analysis: The safety and efficacy of Dupxient® were assessed in 3 randomized, double-blind, placebo-controlled trials (N=2119) that included adults 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 ≥3 in the overall assessment of atopic dermatitis lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 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.

Treatment was administered for 16 weeks. Trial 3 was the concomitant therapy trial where subjects received Dupixent® or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only. The primary endpoint for all 3 trials was the change from baseline to week 16 in the proportion with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints assessed included the proportion with EASI-75 (improvement of ≥75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in peak pruritus from baseline to week 16 in the numeric rating scale (NRS). Results of the primary endpoint were statistically significantly different in trial 1 and 2 ($p<0.001$ for both trials).[2] The table below, adapted from the prescribing information, illustrates results of some outcomes.

	Trial 1		Trial 2		Trial 3	
	Dupixent®	Placebo	Dupixent®	Placebo	Dupixent® & TCS	Placebo & TCS
N for full analysis set	224	224	233	236	106	315
IGA 0 or 1	38%	10%	36%	9%	39%	12%
NNT for IGA 0 or 1 (Calculated by CHC)	4		4		4	
EASI-75	51%	15%	44%	12%	69%	23%
EASI-90	36%	8%	30%	7%	40%	11%
N for subject's w/baseline Peak Pruritus NRS score ≥4	213	212	225	221	102	299
Peak Pruritus NRS (≥4-point improvement)	41%	12%	36%	10%	59%	20%

In trial 3, 353 of the 431 subjects had been in study for 52 weeks at the time of data analysis. Of these 353, responders at week 52 were a mix of subjects who maintained efficacy from week 16 (e.g. 53% of Dupixent® IGA 0

or 1 responders at week 16 remained responders at week 52) and subjects who were non-responders at week 16 who later responded to treatment (e.g. 24% of Dupixent® IGA 0 or 1 non-responders at week 16 became responders at week 52). Results of this analysis can be found in the table below, which was adapted from the prescribing information.

	Dupixent® & TCS	Placebo & TCS	NNT
N	89	264	
Responder at week 16 and 52	22%	7%	
Responder at week 16 but non-responder at week 52	20%	7%	
Non-Responder at week 16 and Responder at week 52	13%	6%	
Non-responder at week 16 and 52	44%	80%	
Overall Responder rate at week 52	36%	13%	5

In all 3 trials, a third randomized treatment arm of Dupixent® 300mg QW did not demonstrate additional treatment benefit over Dupixent® 300mg Q2W.

Place in Therapy: Dupixent® is a subcutaneous injectable monoclonal antibody indicated for the treatment of adults with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. This is the first and only biologic for adults with moderate-to-severe atopic dermatitis. It was found to be effective as compared to placebo for its primary endpoint.

There is evidence that suggests that Dupixent® may be effective for patients who have failed topical therapies, however there are no comparisons found relative to other systemic therapies used for this disease (e.g. oral steroids, cyclosporine). It is therefore recommended that Dupixent® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

☐ **Preferred**
☒ **Non-Preferred**
☒ **Refer to DUR for PA Criteria**

References

[1] Dupixent [package insert]. Bridgewater, NJ: Sanofi-Aventis; AND Tarrytown, NY: Regeneron Pharmaceuticals; 2017.

[2] Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *NEJM*. 2016; 375(24): 2335-2348.