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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Reviewer Name(s) Bob Pratt, Pharm.D.
Acting Team Leader Donella Fitzgerald, Pharm.D.
Acting Deputy Div. Director Jamie Wilkins Parker, Pharm.D.
Review Completion Date January 13, 2017
Subject Evaluation of Need for a REMS

Established Name Dupilumab
Trade Name Dupixent®
Name of applicant Regeneron Pharmaceuticals, Inc.
Therapeutic Class Immunomodulators: Interleukin (IL)-4 and IL-13 antagonist
Formulation(s) 300 mg/2 mL solution
Dosing Regimen Initial dose of 600 mg by subcutaneous injection, followed by 300 mg given every other week.
Table of Contents

EXECUTIVE SUMMARY ............................................................................................................................................................3

1 Introduction ........................................................................................................................................................................3

2 Background .........................................................................................................................................................................3

2.1 Product Information ..............................................................................................................................................3

2.2 Regulatory History .................................................................................................................................................4

3 Therapeutic Context and Treatment Options ......................................................................................................4

3.1 Description of the Medical Condition .............................................................................................................4

3.2 Description of Current Treatment Options .................................................................................................5

4 Benefit Assessment ..........................................................................................................................................................5

5 Risk Assessment & Safe-Use Conditions .................................................................................................................6

5.1 Serious Adverse Events ........................................................................................................................................6

5.2 Severe Adverse Events .........................................................................................................................................7

6 Expected Postmarket Use .............................................................................................................................................7

7 Risk Management Activities Proposed by the applicant .................................................................................8

8 Discussion of Need for a REMS ...................................................................................................................................8

9 Conclusion & Recommendations ...............................................................................................................................8

10 Materials Reviewed ....................................................................................................................................................9

11 Appendices .....................................................................................................................................................................9

11.1 References ..................................................................................................................................................................9
EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Dupixent® (dupilumab) is necessary to ensure the benefits of this product outweigh its risks. Regeneron Pharmaceuticals (Regeneron) submitted a Biologics License Application (BLA 761055) for dupilumab with the proposed indication for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The important identified risk associated with the use of dupilumab is hypersensitivity. The applicant did not submit a REMS with the application but proposed to use routine pharmacovigilance and the approved product labeling as risk minimization measures.

DRISK and the Division of Dermatology and Dental Products (DDDP) agree that a REMS is not needed to ensure the benefits of dupilumab outweigh its risks. Dupilumab showed significant clinical benefit and fulfills an unmet medical need for patients with severe atopic dermatitis. The primary serious risk of the drug is hypersensitivity. Risk management of dupilumab can be accomplished through the use of the labeling.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Dupixent® (dupilumab) is necessary to ensure the benefits of this product outweigh its risks. Regeneron submitted a Biologics License Application (BLA 761055) for dupilumab with the proposed indication for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. This application is under review in the Division of Dermatology and Dental Products. The applicant did not submit a REMS with the application but proposed to use routine pharmacovigilance and the approved product labeling as risk minimization measures.

2 Background

2.1 PRODUCT INFORMATION

Dupixent® (dupilumab), a new molecular entity, is a human monoclonal antibody with a novel mechanism of action that involves binding the interleukin (IL) alpha subunit IL-4Rα shared by IL-4 and IL-13 receptors. Dupilumab is proposed 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. Dupilumab is designed to inhibit downstream signaling of both IL-4 and IL-13, cytokines of Type-2 helper T lymphocytes (Th2) that are believed to play a role in atopic dermatitis and other atopic diseases, such as asthma. Selective inhibition of the Th2 pathway is anticipated to avoid adverse effects typically associated with the use of broad immunosuppressants.

a FDAAA factor (F): Whether the drug is a new molecular entity.
Dupilumab is supplied as a 300 mg/2 mL solution and will be administered subcutaneously by self-injection or by a caregiver. The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections consecutively in 2 different injection sites), followed by 300 mg given every other week.\(^b\)

Dupilumab received Breakthrough Therapy Designation in November 2014 for the proposed indication. Dupilumab is not currently licensed in any other country.

### 2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761055 relevant to this review:

- **11/18/2014:** Breakthrough Therapy Designation granted for treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy or when those treatments are not advisable.
- **03/30/2016:** BLA 761055, Rolling Submission Part 1 of 3, for the treatment of atopic dermatitis received.
- **06/29/2016:** BLA 761055, Rolling Submission Part 2 of 3, for the treatment of atopic dermatitis received.
- **07/29/2016:** BLA 761055, Rolling Submission Part 3 of 3, for the treatment of atopic dermatitis received.
- **11/09/2016:** A Post Mid-cycle meeting was held between the Agency and the applicant via teleconference. The Agency informed the applicant that there were no major safety concerns at this time and there are currently no plans for a REMS.

### 3 Therapeutic Context and Treatment Options

#### 3.1 Description of the Medical Condition

Atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs in children and adults. Multiple factors, including skin barrier abnormalities, up-regulation of type 2 and Th2 immune response, and altered skin resident microbial flora are involved in the pathogenesis of the condition. Moderate-to-severe atopic dermatitis is a serious condition, as skin lesions can encompass a large body surface area (typically 50% and often higher) and patients frequently experience intense and persistent pruritus, sleep deprivation, social embarrassment, anxiety or depression, and a poor quality of life.\(^c\)

Atopic dermatitis follows a chronic relapsing course over months to years, and patients with moderate to severe dermatitis rarely clear without treatment. Patients are also predisposed to the development of secondary cutaneous bacterial, viral, and fungal infections. The National Eczema Association reports there are at least 17.8 million persons in the U.S. with moderate to severe eczema or atopic dermatitis.

\(^b\) FDAAA factor (D): The expected or actual duration of treatment with the drug.
\(^c\) FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

Reference ID: 4042160
and that 3% of adults in the U.S. have moderate to severe eczema/atopic dermatitis requiring systemic therapy.  

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Conventional therapy for atopic dermatitis involves the use of topical emollients, antihistamines, and topical corticosteroids. Long-term use of topical corticosteroids, especially high or super high potency preparations on large body areas may lead to adrenal suppression. Other adverse effects can include skin atrophy, folliculitis, and contact dermatitis, among other effects. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are immunomodulators that can be used as an alternative to topical corticosteroids for the treatment of mild to moderate atopic dermatitis. Rare cases of lymphomas and skin cancer have been reported in patients treated with topical calcineurin inhibitors and long-term continuous treatment is not indicated.  

Adult patients with moderate to severe atopic dermatitis that is not controlled with topical therapy may require phototherapy or systemic immunosuppressant treatment to attempt to manage the disease. Cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine have shown some efficacy in the treatment of severe atopic dermatitis, though the use of these drugs is limited by safety concerns such as hepatotoxicity, bone marrow suppression, and other serious adverse reactions. The use of systemic corticosteroids is not recommended for the long-term management of atopic dermatitis because of an overall unfavorable benefit-risk profile. There is an unmet medical need for a safe and effective treatment for patients with moderate to severe atopic dermatitis for whom topical therapies provide inadequate control.  

4 Benefit Assessment

Three randomized, double-blind, placebo-controlled, pivotal phase 3 studies were conducted in adult patients with moderate to severe atopic dermatitis whose disease was not adequately controlled with topical medication. Two of the studies, R668-AD-1334 (in 671 patients) and R688-AD-1416 (in 708 patients), evaluated dupilumab 300 mg given weekly or every 2 weeks versus placebo over a 16-week treatment period. The third study (R668-AD-1224) was an adjunctive therapy trial in 740 patients that evaluated 52 weeks of dupilumab 300 mg given weekly or every 2 weeks or versus placebo with concomitant use of topical corticosteroids in all study arms. The primary efficacy endpoint in the three studies was the proportion of subjects with an IGA (Investigator Global Assessment) of 0 or 1 (clear or almost clear) and a reduction from baseline of ≥ 2 points at Week 16. Key secondary endpoints included the percent change from baseline to Week 16 in the Pruritus NRS (numerical rating score) and the proportion of patients with an EASI-75 (75% reduction in the Eczema Area and Severity Index) response at Week 16. 

In the two monotherapy studies (R668-AD-1334 and R688-AD-1416), both of the dupilumab dose regimens were superior to placebo at Week 16 for the primary endpoint of IGA success. Of the patients 

\[d\] FDAAA factor (A): The estimated size of the population likely to use the drug involved.  
[e] IGA is the Investigator Global Assessment of eczema severity on a 0-5 point scale.  

Reference ID: 4042160
treated with dupilumab, 36% to 38% achieved the primary endpoint at Week 16 compared with 9% to 10% of patients in the placebo group (p<0.0001 vs. placebo for all treatment groups). For the key secondary endpoints, 36% to 41% of patients achieved a reduction of ≥4 points in Pruritus NRS from baseline at Week 16 in the dupilumab treatment groups, compared with 10% to 12% of patients in the placebo groups (p<0.0001 vs. placebo for all treatment group secondary endpoints). Further, 44% to 53% of patients in the dupilumab groups achieved an EASI-75 response at Week 16 compared with 12% to 15% of patients who received placebo. Similar results were found in R668-AD-1224, with 39% of patients in the dupilumab plus topical corticosteroids (TCS) dose groups achieving the IGA primary endpoint compared with 12% of patients on placebo/TCS; 51% to 59% achieved a ≥4 point reduction in Pruritus NRS compared with 20% on placebo/TCS; and 64% to 69% achieved an EASI-75 response compared to 23% on placebo/TCS (p<0.0001 vs. TCS alone for all dupilumab treatment group secondary endpoints).

The clinical pharmacology reviewer noted that the available data did not show a preferential treatment benefit with dupilumab given weekly compared to given every 2 weeks in any particular subset of patients; the reviewer concluded the dose-response relationship for efficacy overall supports a recommendation of 300 mg given every 2 weeks.

The clinical reviewer concluded that the applicant provided substantial evidence of effectiveness based on the data from the three adequate and well-controlled trials.⁸

5  Risk Assessment & Safe-Use Conditions

The primary safety population was comprised of 1,564 patients who received placebo or dupilumab 300 mg weekly or 300 mg every 2 weeks for 16 weeks of treatment in a placebo-controlled phase 2b dose-ranging study and the phase 3 monotherapy studies.

5.1  Serious Adverse Events

In the atopic dermatitis studies, there were three deaths in dupilumab-treated patients. One of the deaths involved a 49 year-old female with a history of asthma who experienced severe hypoxic ischemic encephalopathy, asthma, and respiratory failure. The second fatal outcome resulted from a completed suicide in a 31 year-old male with a history of depression (including hospitalization) and suicidal ideation, reportedly due to his severe eczema. The third death occurred in a 27 year-old female who suffered a fatal road traffic accident. The clinical reviewer considered the three deaths as unrelated to study drug.

In the primary safety population, the proportion of patients who had a serious adverse event (SAE) other than death during the 16-week treatment period was higher in the placebo group (5% [26/517])

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⁶ The range of response is with reference to the two dose regimens (and the placebo response) in the two studies.
⁸ FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
⁹ Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug

Reference ID: 4042160
compared with the dupilumab 300 mg every 2 weeks group (2.5% [13/529]) and the dupilumab 300 mg weekly group (2.1% [11/518]). The only SAEs that were reported in more than one patient were reported only in the placebo group (sepsis [n=2], suicide ideation [n=3], acute kidney injury [n=2]) or were reported at a higher frequency (atopic dermatitis) in the placebo group [n=9] than in the dupilumab groups [combined n=4]. There were the same number of patients with serious infections in the placebo group (n=5 (1.0%)) as in the dupilumab groups (combined n=5 [0.5%]). The clinical reviewer considered the infections to be unrelated to dupilumab or that a causality determination was compromised by the vagueness of the history.

In an open-label extension study, one patient experienced an SAE of serum sickness that resulted in permanent discontinuation of dupilumab. An additional SAE of serum sickness-like reaction was reported in a phase 2 study that also resulted in permanent discontinuation of the treatment. Both patients recovered without sequelae. The clinical reviewer considered these two cases to be related to dupilumab. There were no additional serious cases of systemic hypersensitivity associated with dupilumab.¹

5.2 SEVERE ADVERSE EVENTS

The proportion of patients in the primary safety population who had at least one severe treatment-emergent adverse event was lower in the dupilumab groups (combined n=41 [3.9%]) compared with the placebo group (n=43 [8.3%]). The Skin and Subcutaneous Tissue Disorders MedDRA SOC had the highest incidence of severe adverse events in the dupilumab groups (combined n=16 [1.5%]) as well as in the placebo group (n=29 [5.6%]). Atopic dermatitis accounted for 13 of the 16 reports associated with dupilumab treatment. Five severe adverse events in the Eye Disorders SOC occurred in the dupilumab groups; three of the severe eye adverse events were reported as conjunctivitis allergic, though none were considered serious and all resolved. Other severe, but non-serious, eye adverse events included one report of blepharitis and one report of ocular hyperemia. Infections categorized as severe were reported in 9 (1.7%) patients in the placebo group and in 6 (0.6%) patients in the combined dupilumab group.

6 Expected Postmarket Use

Dupilumab is likely to be used in the outpatient setting as chronic therapy and will be administered subcutaneously by self-injection or injection by a caregiver. Healthcare professionals will need to provide proper training to patients and/or caregivers on the preparation and administration of dupilumab prior to use according to the Instructions for Use included in the product labeling.

¹ FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
7 Risk Management Activities Proposed by the applicant

The applicant did not submit a REMS with the application but proposed the use of routine pharmacovigilance and the approved product labeling as risk minimization measures.

8 Discussion of Need for a REMS

The clinical reviewer concluded that substantial evidence of clinical efficacy has been established for the use of dupilumab for the treatment of adult patients with moderate to severe atopic dermatitis (AD).

Moderate to severe atopic dermatitis is a serious condition, as skin lesions can encompass a large body surface area (typically 50% and often higher) and patients frequently experience intense and persistent pruritus, sleep deprivation, social embarrassment, anxiety or depression, and a poor quality of life. There is an unmet medical need for a safe and effective treatment for patients with moderate to severe atopic dermatitis for whom topical therapies provide inadequate control. The dupilumab 300 mg dose regimens (with and without TCS) were superior to placebo at Week 16 as measured by the primary and key secondary efficacy endpoints in the three pivotal trials.

Serious adverse events were uncommon. The most serious risk appears to be serum sickness reactions, and the applicant is proposing a warning and precaution for hypersensitivity in the labeling. The proportion of patients experiencing severe adverse events was lower in patients treated with dupilumab compared with placebo. Dupilumab did not appear to increase the number of serious or severe infections. The clinical reviewer noted there is a signal for occurrence of eye disorders with dupilumab, and that the plan is to address this in the labeling. At this time, this reviewer is not recommending a REMS for the management of the risks of dupilumab therapy.

9 Conclusion & Recommendations

Based on the available data, DRISK believes risk mitigation measures beyond professional labeling are not warranted for dupilumab and a REMS is not necessary to ensure the benefits outweigh the risks. Serious adverse events associated with dupilumab were uncommon, and severe adverse events were more frequently reported in patients who received placebo than in those treated with dupilumab.

Should DDDP have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.
10 Materials Reviewed

The following is a list of materials informing this review:

5. BLA 761055 Dupixent (dupilumab) injection, 150 mg/mL Regeneron Pharmaceuticals, Mid-Cycle Meeting Agenda and Notes, October 28, 2016.
7. Carr, B., Division of Dermatology and Dental Products, email communication, December 20, 2016.

11 Appendices

11.1 References

1 Weston WL and Howe W. Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis (eczema). In:UpToDate, Dellavalle RP, Levy ML, Fowler J, Corona R (Eds), UpToDate, Waltham, MA 2016.


3 Weston WL and Howe W. Treatment of atopic dermatitis (eczema). In:UpToDate, Dellavalle RP, Levy ML, Fowler J, Corona R (Eds), UpToDate, Waltham, MA 2016.

4 Spergel JM. Management of severe refractory atopic dermatitis (eczema). In:UpToDate, Dellavalle RP, Levy ML, Fowler J, Corona R (Eds), UpToDate, Waltham, MA 2016.
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/s/

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