4-2020

The Proposed Formulary Status and Evidence-based Use of Dupilumab (Dupixent®) for the FDA Approved Treatment of Asthma

Katelyn Stuart
Ohio Northern University

Alexis Miller
Ohio Northern University

Katelyn Koebel
Ohio Northern University

Karen Kier
Ohio Northern University

20th Annual National Student Pharmacist
P&T COMPETITION | 2020
HELD DURING AMCP2020 • APRIL 21–24, 2020
GEORGE R. BROWN CONVENTION CENTER • HOUSTON, TX

AMCP Foundation

Drug Monograph

Team 20054

Patients First Health Plan
Formulary Drug Monograph

Generic Name:	**dupilumab**
Brand Name:	**DUPIXENT®**
Manufacturer:	**Regeneron Pharmaceuticals, Inc./sanofi-aventis U.S. LLC**
Date of Review:	**January 27, 2020**
Purpose:	**FDA approved; consider new indication**
Indication:	**Add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma**

Therapeutic Alternatives

Agents in the Same Pharmacologic Class

Preferred/Formulary	Nonpreferred/Nonformulary
	Fasenra®
	Nucala®
	Xolair®

Agents in a Different Pharmacologic Class

Preferred/Formulary	Nonpreferred/Nonformulary
Fluticasone	Albuterol sulfate
Montelukast	Beclomethasone dipropionate
Salmeterol	Mometasone furoate

Table of Contents

(Ctrl + Click to follow any link below to view the section.)

Executive Summary

Evidence Gaps

Value and Operational Matrix

Recommendations to the Committee

Clinical Evidence Evaluation
Efficacy
Safety
Comparative effectiveness
Value proposition
Patient subgroups

Economic Evidence Evaluation

Clinical Evidence Tables

Cost-Effectiveness Evidence Summary

Background
Disease background
Treatment alternatives
Product background

Methodology

References

Abbreviations used in this monograph:			
ACQ	Asthma control questionnaire	IL	Interleukin
ACQ-5	Five question asthma control questionnaire	LABA	Long-acting beta 2 agonist
AE	Adverse event	MCID	Minimal clinically important difference
AWP	Average wholesale price	NNT	Number needed to treat
CBC	Complete blood count	OCS	Oral corticosteroid
CDC	Centers for Disease Control	PMPM	Per member per month
CEPAC	Comparative Effectiveness Public Advisory Council	QALY	Quality-adjusted life-year
FeNO	Fraction exhaled nitric oxide	q2w	Every two weeks
FEV_1	Forced expiratory volume in 1 second	SOC	Standard of care
ICER	Institute for Clinical and Economic Review	SUBQ	Subcutaneous injection
IgE	Immunoglobulin E	US	United States

Executive Summary

Efficacy in Clinical Trials (Strength of Evidence: Medium)

Dupixent® decreased the risk of an asthma related exacerbation in the overall population treated when compared to the placebo group in treatment. Dupixent® also increased the FEV_1 value in the overall treated population when compared to the placebo group. The improvements of the FEV_1 were seen within 2 weeks, but then were still apparent over 52 weeks after the last treatment.[1] Studies typically focus on the number of exacerbations and FEV1 values for considering the efficacy of Dupixent® in the target patient subgroups. In comparison to the current treatments available, including inhaled corticosteroids and LABAs, Dupixent® provides greater efficacy in the treatment of moderate-to-severe asthma, increasing quality of life and patient outcomes.[1]

Reason for evidence grade: Dupixent® trials were powered for number of exacerbations and the FEV_1 values of Dupixent® treatment group when compared to the placebo group. However, while in the trials, patients were still using inhaled corticosteroids and LABAs, which could alter the results of the treatment when compared to the placebo.[1]

Safety in Clinical Trials (Strength of Evidence: Low)

Studies report minimal discontinuation of Dupixent® due to adverse effects. Common adverse events experienced were upper respiratory tract infections and injection site reactions. Other less common adverse events consisted of headache, nasopharyngitis, and bronchitis.[1]

Reason for evidence grade: Since Dupixent® was recently approved, no long-term safety data exists. Additionally, no information is present on the use of Dupixent® in pregnant women. Minimal safety data has been identified, however extensive powered safety trials have not been completed. In safety trials, the trials are not powered due to small numbers. Post-marketing safety data from phase IV trials will be of more value.[1]

Real World Comparative Effectiveness (Strength of Evidence: Low)

No comparative or effectiveness evidence is published for Dupixent® for asthma, however real world evidence for atopic dermatitis has been established.

Reason for evidence grade: No comparative or effectiveness evidence exists for Dupixent® for Asthma.

Value Proposition (Strength of Evidence: High)

Based on the CDC-reported asthma prevalence in 2016 and the prevalence of persistent asthma, Patients First Health will supply a maximum of about 43,000 patients falling under the Dupixent® indication for asthma. With the introduction of Dupixent® among this patient subgroup, the projected decrease in PMPM in year 1 is $0.0017 and up to $0.0175 in year 5.[1] The maximum cost savings of introducing Dupixent® in our calculated patient prevalence would be $72.96 in year one and about $751.09 in year 5. According to data

from the Institute of Clinical and Economic Review, the US exacerbation cost resulting in emergency department visits, hospitalization, and steroid therapy was averaged to $12,634 per patient.[2] Results for the Liberty Asthma Quest study found that Dupixent® reduced the probability of asthma exacerbations by about 50% when compared with placebo (RR of 0.523 for the 200mg dose). The NNT in order to meet this reduction was 2.[1] The study found that Dupixent® use was able to reduce exacerbation related hospitalization in half as well, with a NNT of 34. We calculated that Dupixent® therapy can therefore reduce Patients First Health's medical plan costs related to exacerbations resulting in hospitalization by about $16 million per year, assuming all eligible patients were treated and had 2 annual exacerbations. In the Liberty Asthma Venture trial, Dupixent® was found to decrease OCS dose to less than 5 mg/day in 70% of treated patients compared to one third of placebo. NNT calculated to reach this was 3. Almost 50% of Dupixent® treated patients even completely eliminated OCS use by the end of the study.[1] The annual cost for the long term use of OCS, including treatment of AE's was $7,983.[2] Dupixent® can decrease the cost of prescription drug treatment with steroids and medical costs of treating any adverse effects resulting from OCS use. Additionally, Dupixent® is the only biologic that is used only by self-administration. Xolair® and Cinqair® are required in office administration and Fasenra® and Nucala® have the in office option.[3,4,5,6,7] The averaged in office based physician charge for administration was $74.16, not including the cost of the drug. Cinqair® is an IV therapy, so would have a higher cost of $144.72. Dupixent® would eliminate in office charges and would only require the plan to cover the prescription drug cost. We concluded that there would be no additional monitoring price per patient for Dupixent® therapy. Blood eosinophil count would be the major monitoring parameter needed, but patients with the indication will be required to monitor their asthma with routine parameter including testing a CBC regardless of Dupixent® treatment. Further economic evaluations should be studied to simulate more real-world treatment scenarios.

Target Patient Subgroups (Strength of Evidence: Medium)

Patients enrolled in the Liberty Asthma Quest study were required to be at least 12 years old with a diagnosis of asthma for more than one year, who were currently being treated with a medium to high dose ICS and 1 or 2 controller treatments for over three months and 1 month of consistent dosing. Patients ACQ-5 scores were greater than 1.5 at baseline and had worsening asthma, resulting in hospitalization or treatment with a systemic corticosteroid within the past year, but no earlier than 1 month before baseline visit. Excluded patients included those with other lung diseases, obesity, and current or past smokers.[1] Studies found that patients with a blood eosinophil count of greater than 300 cells/μL resulted in better outcomes than patients lower eosinophil levels. Other subgroups that showed better outcomes include patients with at least two exacerbations in the past year, those with an ACQ-5 score greater than or equal to 1.5, and chronic OCS users.[2] Not all studies were powered for these subgroups, but they were found to be more cost-effective due to having a higher probability of better outcomes than other subgroups. Post-marketing studies of Dupixent® use in the indicated asthma patients should be evaluated to find significant evidence towards treating these specific patients.

Evidence Gaps

Population

The mean age in the Liberty Asthma Quest and Liberty Asthma Venture trials was around 50 years old, with about 40% of patients being male.[1] The clinical trials studying Dupixent® in moderate to severe asthma patients have good external validity of Patients First Health Plan membership. The majority of covered

patients in this health plan fell in the 18-64 year old range and were evenly distributed among gender. We find no relevant evidence gap of the population studied in clinical trials for Dupixent®. Patients First Health Plan also mostly covers patients aged 12 years and older, the indicated age for Dupixent® use, with only 16% of patients being below 12. The use of competitor, Xolair®, in pediatric patients aged 6 and up is not as clinically relevant to the patient demographic in our membership.

Intervention

The self administration of subcutaneous injections could potentially decrease compliance for patients who have a fear of needles. With the Dupixent® prefilled syringe, patients are able to see the needle, unlike auto injection devices, increasing the likelihood that patients with a fear of injections will not be fully compliant with the injections. The dosing frequency of q2w subcutaneous injection may not be the most practical for patient compliance compared to less frequent dosing seen with competing injections. Xolair® and Nucala® may be given every 4 weeks and Fasenra® every 8 weeks. Fasenra® and Nucala® are also available as autoinjectors. Xolair® has pediatric indications, so patients less than 12 years old could use it.[3,4,5,6,7] The most common side effect, injection site reactions, may discourage patients use. Dupixent® can be administered to a larger area compared to Fasenra® and Nucala®, which could decrease the frequency of injection site reactions if properly injected to different areas. Patients may be able to use Dupixent® therapy for the treatment of multiple disease states. Dupixent® is indicated for atopic dermatitis and chronic rhinosinusitis with nasal polyposis as well, while Fasenra® only has indications for asthma.

Comparator

There are currently no studies powered for direct head-to-head comparison of Dupixent® to anti-IL-5 monoclonal antibodies or other alternatives.[8,9] Regeneron Pharmaceuticals researched the safety and efficacy of Dupixent® versus other asthma therapies.[10] The study focused on uncontrolled persistent asthma and OCS-dependent asthma. In one meta-analysis, Dupixent® was compared to results of Fasenra®, lebrikizumab, Nucala®, Cinqair®, tralokinumab and placebo. Dupixent® showed the greatest increase in FEV_1 and asthma quality of life scores. It also had the second best reduction in asthma control questionnaire scores, following Nucala®.[3,4,5,6,7,9]

Outcome

Results in the uncontrolled persistent asthma evaluation concluded that Dupixent® typically has greater outcomes for FEV_1, while Xolair® and Nucala® have not shown consistent improvements. Dupixent® had better efficacy than Xolair®, Nucala®, Fasenra® and Cinqair® in terms of NNT. Dupixent® 300mg was significantly better than Xolair® 150 to 375 mg. There was a numerical advantage of Dupixent® in the OCS-dependent trial versus Nucala® and Fasenra®. Although Dupixent® had higher outcomes in terms of FEV_1 and quality of life than the alternative therapies, in the meta-analysis mentioned above there was no statistically significant evidence that Dupixent® was preferred for the outcomes.[9] It is important to note that of all these therapies, only Dupixent® and Cinqair® were able to significantly lower exacerbations. Dupixent® stands out from these drugs because it has the ability to block both the IL-4 and IL-13 receptors, rather than only one IL receptor. [3,4,5,6,7,9]

Time Frame

Asthma is a chronic condition that patients will treat for most of their lives. The longest treatment period for any clinical trial of Dupixent® q2w dosing lasted 52 weeks, with a 12 week follow up, seen in the Liberty Asthma Quest.[1] A year long study is not sufficient enough to determine the long term effects of Dupixent®, which could potentially be a life-long drug for patients. Commonly with this class of drugs, patients can develop antibodies, making the drug less clinically effective at the given dose. Dupixent® does show results within 2 weeks, so having a year long study was able to accurately assess the short term benefits of the drug. More extensive studies are needed in order to fully determine its efficacy and safety in long term use.[1]

Important Questions That Remain Unanswered

1. What is the long-term safety of Dupixent® post-marketing surveillance?
2. At what frequency do patients develop monoclonal antibodies to Dupixent® treating asthma (2% developed neutralizing antibodies with atopic dermatitis per FDA reporting)?
3. Is there any documentation of patients becoming refractory to Dupixent®? If so, do the comparator drugs still work in these patients?
4. Is this a medication that could be efficacious as maintenance therapy that is administered less frequently than every two weeks?
5. What happens when a patient stops or is nonadherent to Dupixent® therapy? Can Dupixent® or another competitor be resumed and still maintain efficacy?
6. Would decreasing the frequency of Dupixent® dosing affect the long-term safety of the therapy?
7. Does Dupixent® decrease overall hospitalization rates as a powered outcome variable in effectiveness studies?
8. What is the efficacy and safety of Dupixent® for children with severe asthma under the age of 12?

Value and Operational Matrix

How much does this product improve over the current standard of care?	☐ Cure ☐ Substantial ☒ Modest ☐ Minimal ☐ None
Other societal considerations	Dupixent® allows for self-administration.
Incremental cost-effectiveness ratio (ICER)	$351,000/ QALY
Formulary recommendation	☒ Definite include

	The medication is safe and effective for its indicated use and offers a clinical benefit not available by any other medication on the market. ☐ Optional include *The medication is safe and effective for its indicated use, but other clinically equivalent alternatives are available.* ☐ Do not include *The clinical benefits of the medication do not outweigh the cited safety risks.*
Budget Impact	
Projected spend:	$31,000 (excluding the loading dose for the first year)
$ PMPM impact:	-$0.0017 PMPM -$72.96 PMPM in year 1 -$751.09 PMPM in year 2
Utilization Management Considerations	
Prior authorization recommended?	☒ Yes ☐ Maybe ☐ No
Step therapy?	☐ 1st ☐ 2nd ☐ 3rd ☒ No
Quantity limit?	Two pens per 30 days.

Recommendations to the Committee

Dupixent® for subcutaneous use in moderate-to-severe asthma patients is one of few biologics currently FDA approved for its indication, but it is the only biologic agent that targets the IL-4 pathway. This new mechanism of action presents a new dual therapy, targeting both IL-4 and IL-13.

Compared to other biosimilars, Dupixent® is the only drug that can treat both atopic dermatitis and nasal polyps, in addition to asthma. It can be administered at home, which may save patients money by avoiding office-based physician charges. It offers the greatest convenience for the price, making it a strong contender in the treatment of severe asthma.

Therefore, the following P&T Committee actions are recommended.

- Include Dupixent® subcutaneous injection every 2 weeks for the treatment of moderate-to-severe asthma with an eosinophilic phenotype or OCS-dependent asthma as a 4th tier specialty drug on the Patient First Health Plan formulary
    - o preferred formulary inclusion of injection covered under the pharmacy benefits with an approved prior authorization
- Fasenra®, Nucala®, and Xolair® will remain a non-preferred specialty brand requiring prior authorization with quantity limits

- Dupixent® will be preferred over other biologic therapies due to high potential cost saving in the Patient First Health Plan medical and pharmacy benefits
    - Dupixent® decreases medical costs due to decreased exacerbations and decreased in office visits/injections requiring health care professional administration and observation.
    - Pharmacy benefits include medication provided by self-administration and follow-up from Patient First Health Plan to assess adherence to therapy prior to dispensing.
- Another review should be completed next year to determine any new biologics or other therapies and changes in price. Consider any new data such as post-marketing effectiveness and safety.
- A prior authorization should be placed on Dupixent® before coverage is approved
    - Prior authorization description on the next page
    - A quantity limit of the monthly dose of Dupixent® should be approved
        - 2 single-dose pens per 30 day period
        - If higher dose or other criteria not in the prior authorization is prescribed, prescriber must submit paperwork to support their decision with evidence. Medical directors of Patient First Health Plan will review evidence. If medical directors deny claim, the claim will go to external review.
    - Within the prior authorization, patients must fail SoC therapy, with exceptions, to be considered for approval
- A patient adherence program should be implemented to monitor patients use to determine further authorization and cost effectiveness for patients
    - Patient must be at least 80% adherent or reauthorization should not be granted to avoid potential loss of effectiveness
    - Patients who are adherent who seem to become resistant will be tested for neutralizing antibodies and approved for non-formulary alternatives.

Coverage Criteria: Dupixent® (dupilumab)

FDA-Approved Indication

IL-4 receptor antagonist indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥12 years with an eosinophilic phenotype or with OCS-dependent asthma.

Criteria for Prior Authorization

DUPIXENT® will be considered for coverage under the pharmacy benefit for the indication of asthma when the following criteria are met:

- Individual is aged ≥12 years AND

- Individual has a diagnosis of moderate-to-severe eosinophilic asthma as demonstrated by the following:
    - A pretreatment FEV_1 less than or equal to 80% predicted AND
    - FEV_1 reversibility of at least 12% and 200 mL after albuterol administration AND
- One of the following:
    - Individual has a blood eosinophil count (in the absence of other potential causes of eosinophilia, including hypereosinophilic syndromes, neoplastic disease, and known or

suspected parasitic infection) greater than or equal to 300 cells/microliter at initiation of therapy; AND
- Individual has had a 3-month trial and inadequate response or intolerance to medium-to-high dose inhaled corticosteroid

OR

- Individual has oral corticosteroid dependent asthma; AND
- Individual has had a 3-month trial and inadequate response or intolerance to high dose inhaled corticosteroid with daily oral glucocorticoids given in combination with a controller medication (either a LABA, or leukotriene receptor antagonist, or theophylline)

OR

- Individual has an eosinophil count of less than 300 cells/microliter; AND
- Individual has had 3 month trial and inadequate response or intolerance to medium-to-high dose inhaled corticosteroid given in combination with a controller medication (either a LABA, or leukotriene receptor antagonist, or theophylline)

- Individual has experienced two or more asthma exacerbations in the prior 12 months requiring use of systemic corticosteroid or temporary increase in the individual's usual maintenance dosage of oral corticosteroids.

DUPIXENT® will be considered for coverage under the pharmacy benefit for the indication of atopic dermatitis based on published studies when the following criteria are met:
- If the patient is refractory to at least 2 other medications for atopic dermatitis
-

DUPIXENT® will be considered for coverage under the pharmacy benefit for the indication of chronic rhinosinusitis with nasal polyposis based on FDA indication approval when the following criteria are met:
A patient has been diagnosed with chronic rhinosinusitis with nasal polyposis

Length of Initial Approval

- 12 months

Reauthorization Criteria

If the individual has experienced one or more of the following:
- Decreased use of rescue medication
- Decreased frequency of exacerbations
- Decreased yearly hospitalizations or medical care
- Increase in predicted FEV_1 from the baseline before treatment
- Fewer reported symptoms related to asthma

Then patients will be eligible for reauthorization.

If patients does not demonstrate >80% medication adherence, then reauthorization will not be granted.

Exclusions

- Parasitic helminth infections
- Pregnancy
- Children under the age of 12

Clinical Evidence Evaluation

Efficacy

Dupixent® significantly decreased the percentage risk of an asthma-related exacerbation in the study by Wenzel, et al., with 44% of the placebo group experiencing an exacerbation in the 12-week period while 6% of the Dupixent® treated group experienced an exacerbation.[10] In the study from Wenzel, et al., the percentage change in mean of FEV_1 from the baseline was 7.01% in the placebo, however in the dupilumab treatment group, the percentage change in mean of FEV_1 ranged from 14.52% to 17.34%.[9] Dupixent® decreased the number of employed patients with greater than one day of sick leave due to severe exacerbation events from 11 people in the placebo group to only 5 in the Dupixent® treated group in a 24 week study.[11] As proved in the study by Corren, the change from baseline predictions for FEV_1 in the treatment with Dupixent® was -0.60. In comparison to the expectations of the MCID at week 24, 76.7 out of 307 patients while only 60.1 of 158 patients exceeded in the placebo group.[12] LIBERTY ASTHMA QUEST analyzed the risk reduction percent with a 95% confidence interval in comparison to the placebo, and in Dupixent® 200mg every 2 weeks, the relative risk reduction was statistically significant at 48-78%, depending on the number of exacerbations in the previous year. In Dupixent® 300 mg q2w, the relative risk reduction was statistically significant at 46-64%, also depending on the number of exacerbations in the previous year.[1]

Real World Comparative Effectiveness

No comparative or effectiveness evidence is published for Dupixent® for asthma, however real world evidence for atopic dermatitis has been established. Post-marketing surveillance data will help to define real world effectiveness. Since the biologics are a high research and development expense for the manufacturers, it is unlikely that comparison data will be published.

Safety

Safety data for the use in asthma is not widely available at this time due to Dupixent®'s recent approval for the indication of asthma. Most clinical studies have not found any consistent major adverse effects. The primary adverse effects are injection site irritation and upper respiratory tract infections; however, it is uncommon for these adverse reactions to be severe enough for a patient to drop out of the trial.[1] Because Dupixent® for asthma has not been studied for its use in the real world, much of the severe safety concerns are left unknown. In the studies observed, the largest sample size was 774 individuals who met a certain criteria to be included in the study. Many safety observations will not be apparent until after thousands of people are using the drug and rare adverse effects, including those that have roughly a 1 in 10,000 chance of occurring, are being reported It is important to note that one study found that a slightly higher incidence of

any reported adverse effect in the placebo group than the treatment group.[13] The only current drug interaction is live vaccines.[14]

Serious Adverse Events

Upper respiratory tract infections and bronchitis occurred in some patients while taking dupilumab. Influenza was also noted in some participants, but there was a higher incidence of influenza in the placebo group than the treatment groups. It has been shown that patients with elevated eosinophil levels are more likely to have eosinophilia while on Dupixent®.[1,13]

Other Adverse Events

The most common side effect of dupilumab is injection site reactions, which occurred in approximately 9% to 21% of participants in one study. Minor side effects included conjunctivitis, headache, and sinusitis.[14]

Tolerability

Dupixent® has been well tolerated in the treatment of asthma. Injection site reactions seem to be the largest concern for patient adherence. One study found that patients on the 200 mg dose were significantly less likely to discontinue therapy than the 300 mg dose, possibly due to fewer adverse effects.[1]

Patient Subgroups

Patients most suitable for Dupixent® have a blood eosinophil count of greater than or equal to 300 cells/uL, at least two exacerbations in the prior year, and an asthma control questionnaire score greater than or equal to 1.5.[2] Another subgroup that has the indication would be those that have chronis OCS use.[2] Important biofactors in asthma other than blood eosinophils are FeNO, serum total IgE and eotaxin-3. FeNO, regulated by IL-13, is a sign of epithelial inflammation. Dupixent® works to inhibit IL-13 and thus lower the inflammation. This is tested by exhaling slowly into a portable device. The results are recorded in parts per billion. One trial observed a decrease in FeNO in two weeks while taking Dupixent®.[1] IgE, an antibody that helps fight infection and stimulate mast cells, has also shown a gradual reduction while taking Dupixent®. It can be found in a blood test. Eotaxin-3 helps regulate eosinophil migration in the airways. It is associated with increased asthma exacerbations and a lower FEV_1. The use of an enzyme-linked immunosorbent assay. In this trial, plasma eotaxin-3 decreased, which may be partly responsible for fewer asthma exacerbations.

Economic Evidence Evaluation

Pharmacoeconomic data was found from the Institute for Clinical and Economic Review. There were no other economic data found in literature comparing Dupixent® with other therapies. The ICER model found Dupixent® to be cost effective using a budget impact model and cost-effectiveness studies, comparing Dupixent® therapy to SoC and other biologics indicated for the treatment of asthma. Asthma and Allergy Foundation of America survey found that the two most important factors for choosing a therapy for patients with asthma included effectiveness and cost, with the former being far more important, but the cost was the number one issue with adherence.[2] Eliminating overall cost for patients will be able to increase patient adherence and ultimately decrease the cost of treatment for the health plan. The manufacturer's dossier found the average cost of Dupixent® for patients on other health plans. With insurance in place for patients, cost for

commercial insurance members averages to $100, Medicare members are responsible for 25% of the cost, and an average of $8 for Medicaid members. The AWP for one dose of Dupixent®.[14] $1,811.7 for both the 200 and 300 mg doses prefilled syringes. The first year would have an additional dose cost, due to the initial loading dose.

ICER analyzed a long term cost effectiveness study based on previous Markov models for assessing cost-effectiveness, including ICER's Nucala® report and NICE's Xolair® report. The model compared the 5 biologic therapies to reflect a lifetime horizon scenario. ICER further created and analyzed a potential budget impact model based on US census and CDC prevalence reports. The budget impact was a 5 year model that found Dupixent® to be cost-saving compared to the current treatment mix.[2]

Value Proposition

Summary of Product Value

Patients eligible for treatment with Dupixent® in Patients First Health Plan estimates to 43,000 people, calculated based on plan demographics and the US census and CDC prevalence data. Based on these calculations and the calculations from executive summary, there was a net reduction per patient in overall health plan costs of adding Dupixent®. Populations that may benefit more from Dupixent® therapy, including higher eosinophil counts, ACQ scores, and greater number of exacerbations would have an effect on the net savings as well, although are not included in the calculations or ICER analyses.

Dupixent® is indicated for atopic dermatitis, chronic rhinosinusitis with nasal polyposis, as well as asthma. It is common for these conditions to be comorbid in patients, and therefore it could be possible for Dupixent® to treat multiple conditions with one treatment dose. The only other two biologics with other indications include Nucala® for eosinophilic granulomatosis with polyangiitis and Xolair® for chronic idiopathic urticaria. Some other societal economic considerations included cost of in office based physician charges and the effect of patients missing work for asthma related burdens. Dupixent® reduces the cost of in office based charges due to its self-administration only regimen, compared to all other biologics, which will have some form of in office requirements. The ICER cost effectiveness studies found that there are less hours missed per week of work for patients who are on biologics compared to the SoC. The self-administration of Dupixent® presents patients with an opportunity for increased access compared to in office visits, but could risk causing decrease in adherence. Regardless, the midwest CEPAC voting determined that self-administration still presents as a net positive for patients. Based on evidence from manufacturing of Xolair® , biologic therapies were found to reduce the average number of hours of work missed per week compared to the SoC, potentially increasing our patients budget in order to afford the therapies.[2]

Incremental Cost-effectiveness

ICER estimated cost-effectiveness of Dupixent® compared to SoC using a Markov model. They studied reductions in annual exacerbation rates resulting in outpatient steroid bursts, emergency department visits, and hospitalizations. The health states followed from start of treatment until death included asthma non-exacerbation state (day to day symptoms), asthma exacerbation state, and death. Baseline characteristics were averaged to eliminate difference that would affect outcomes of cost. The long-term cost effectiveness model compared the 5 biologic treatment options based on QALY and annual prices from manufacturers. Dupixent®'s cost effectiveness ratio was $351,000/QALY and annual price of $31,000. The ratio was near the average of the biologics, with Xolair® being lowest at $325,000/QALY and reslizumab being highest at $391,000/QALY. The annual price of Dupixent® was highest, compared to benralizumab at the lowest of $27,800 per year. The model assumed that costs and outcomes to be discounted to 3% per year. Limitations to this model were based around lack of evidence involving long-term studies on treatment or discontinuation rate and lack of evidence for subpopulations.[1]

Summary of incremental cost-effectiveness ratios found by studies included in this review.
Base-case incremental cost effectiveness ratio for Dupixent® is $351,000/QALY.

Budget Impact
ICER used a five-year model, based on the cost-effectiveness, to estimate costs and impact of Dupixent® displacing other biologics from the market. The model estimated the potential population eligible for Dupixent® use (237,000 patients per year) by using population data. The estimates were based on the US consensus and CDC prevalence data of asthma. The model compared Dupixent® therapy to the current treatment mix, which consists of 27% biologic therapy and 73% SoC. Current market share estimates among biologic therapies for the treatment of asthma include 1.8% reslizumab, 5.2% benralizumab, 18.2% mepolizumab, and 74.9% omalizumab. Xolair® is the main competitor for Dupixent® in the budget impact model. Based on an annual WAC, Dupixent® costed about $1,400 more than the current treatment mix. Annual net price resulting in per patient savings of about $5,700 and all cost effective QALY thresholds resulted in cost savings ranging from $22,000 to $31,000.[1]

Clinical Evidence Tables

Reference: Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet Respir Med*. 2016 Jul 2;388(10039):31–44.

Study Design and Evidence Grade	Drug Regimens	N	Time Horizon	Study Population	Endpoints	
					Primary	Secondary
Phase IIb DB/PC	- Placebo - Dupixent®, 200 mg - Dupixent®,300 mg (all SUBQ)	776	24 weeks 2 weeks/4 weeks	Adults 18 years of age or older with - Asthma diagnosis for the past 12 months or more - Medium-to-high dose inhaled corticosteroid treatment and long-acting B2 agonist at least 1 month before screening - FEV1 of 40-80% - 5-item Asthma Control Questionnaire score of 1-5 or higher - Reversibility of at least 12% and 200 mL	FEV1 compared in patients with baseline blood eosinophil counts of at least 300 eosinophils per microliters.	Eosinophil count of at least 300 eosinophils per microliter

Efficacy/Effectiveness

Dupilumab vs. Placebo in overall population (n=776)

	Placebo	Dupilumab, 200 mg/4 weeks	Dupilumab, 300 mg/4 weeks	Dupilumab, 200 mg/2 weeks	Dupilumab, 300 mg/4 weeks
N (%)	n=158	n=154	n-157	n=150	n=157
Greater than 1 exacerbation in the 24 week period	41 (26)	23 (15)	28 (18)	13 (9)	17 (11)
LS mean change in FEV1 from baseline at week 24 (%)	7.01	14.52	15.68	16.62	17.34
Risk reduction vs. placebo (%)	-	53.7	33.2	70.0	70.5
P value vs. placebo	-	0.0093	0.1380	0.0002	0.0001

Serious Adverse Events

	Dupilumab Regimens	PBO
N (%)	n=611	n=158
AE leading to discontinuation	27 (4)	5 (3)
Upper respiratory infection	83 (14)	28 (18)
Injection site reaction	79 (13)	12 (8)
Headache	62 (10)	20 (13)
Nasopharyngitis	59 (10)	15 (9)
Bronchitis	51 (8)	16 (10)
Influenza	38 (6)	5 (3)
Sinusitis	36 (6)	11 (7)

Weaknesses Impacting Internal/External Validity

- Short duration of the study in patients with uncontrolled persistent asthma
- Small number of patients per dose regimen
- Study not powered to directly compare the different dosing levels of dupilumab
- Approved treatment options remain limited

Reference: Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in Persistent Asthma with Elevated Eosinophil Levels. *New England Journal of Medicine*. 2013;368(26):2455–66.

Study Design and Evidence Grade	Drug Regimens	N	Time Horizon	Study Population	Endpoints	
					Primary	Secondary
Phase 2A PC, PG, DB, RCT	- Placebo - Dupilumab, 300mg (SUBQ) - Fluticasone, 250 or 500 ug - Salmeterol, 50 ug	104	12 weeks	- 18-65 years of age - Moderate to severe asthma - Blood eosinophil count of at least 300 cells per microliter - Sputum eosinophil level of at least 3% - Medium to high dose inhaled glucocorticoids usage - Long acting beta agonist usage	- Occurence of an asthma exacerbation	- Occurence of an asthma exacerbation - Estimate for asthma exacerbation - Change in FEV1 baseline - Change in morning PEF - Change in evening PEF - Change in ACQ5 score - Morning asthma symptom score - Evening asthma-symptom score - Number of nocturnal awakenings - SNOT-22 score - Number of inhalations of albuterol or levalbuterol in 24 hour period

Efficacy/Effectiveness

	Placebo	Dupilumab
N (%)	n=52	n=52
Occurence of exacerbation during 12-week intervention period	23 (44)	3 (6)
Greater than 30% reduction in morning PEF from baseline on 2 consecutive days	10 (19)	1 (2)
Greater than 6 inhalations of albuterol or levalbuterol in a 24-hour period relative to baseline on 2 consecutive days	10 (19)	1 (2)
Kaplan-Meier estimate for probability of asthma exacerbation at 12 weeks (95% CI)	0.46 (0.32 to 0.60)	0.06 (0.00 to 0.12)
Change in FEV1, baseline to week 12	-0.22 +/- 0.06	0.05 +/- 0.06

Serious Adverse Events

	Placebo	Dupilumab
N (%)	N=52	N=52
Any adverse event	40 (77)	42 (81)
Any serious adverse event	3 (6)	1 (2)
Study discontinuation owing to adverse event	3 (6)	3 (6)
Death	0	0
Injection site reactions	5 (10)	15 (29)
Nasopharyngitis	2 (4)	7 (13)
Upper respiratory tract infection	9 (17)	7 (13)
Headache	3 (6)	6 (12)

(liters)		

Nausea	1 (2)	4 (8)
Arthropod bite	0	3 (6)
Muscle spasms	0	3 (6)
Nasal congestion	1 (2)	3 (6)
Rash	1 (2)	3 (6)
Viral upper respiratory tract infection	0	3 (6)
Sinusitis	5 (10)	1 (2)
Gastroenteritis (viral)	3 (6)	0
Rhinitis, seasonal	3 (6)	0

Weaknesses Impacting Internal/External Validity

- Short duration of the study in patients with uncontrolled persistent asthma
- Small number of patients per dose regimen

Reference: Corren JN, Castro MM, Chanez Pundefined, Fabbri Lundefined, Joish Vundefined, Amin Nundefined, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. *Eur Ann Allergy Clin Immunol*. 2019;122(1):41–9.

Study Design and Evidence Grade	Drug Regimens	N	Time Horizon	Study Population	Endpoints	
					Primary	Secondary
Phase IIb Dose ranging, RCT, DB, PC, PG	-200 mg Dupilumab - 300 mg Dupilumab (Both SUBQ)	465	24 weeks	- Adults with asthma diagnosis for 12 months or longer - Treatment with medium to high dose ICS+LABA with a stable dose for 1 month or longer before screening - FEV 40-80% of predicted with reversibility of at least 12% - 5-item ACQ-5 score of 1.5 or higher at baseline	- Eosinophil count less than 300 and at least 300 cells per microliter	- Eosinophil count less than 300 and at least 300 cells per microliter - Changes from baseline at week 24 for ACQ-5, AM and PM asthma scores, and AQLQ total scores

Efficacy/Effectiveness

	Placebo	Dupilumab, 200 mg/2 weeks	Dupilumab, 300 mg/2 weeks
N (%)	n=158	n=150	n=157

Serious Adverse Events

- Injection site reaction
  - 20% Dupilumab 200
  - 26% Dupilumab 300
  - 13% Placebo

Weaknesses Impacting Internal/External Validity

Total number of severe exacerbation events	75	20	23
Number of employed patients with greater than one day of sick leave due to severe exacerbation event	11 (11.8)	4 (4.9)	5 (5.7)
Proportion of patients meeting or exceeding the MCID (ACQ-5 total score)	60.1	76.7	72.6

- Short duration of the study in patients with uncontrolled persistent asthma
- Small number of patients per dose regimen

Reference: Dupixent. Sanofi and Regeneron Pharmaceuticals, Inc. edossier AMCP P&T Competition.https://www.amcpfoundation.org/student-pharmacists/amcp-foundation-annual-pt-competition/2020-p-t-competition. 2019.

Study Design and Evidence Grade	Drug Regimens	N	Time Horizon	Study Population	Endpoints	
					Primary	Secondary
IIB, pivotal RCT, DB, PC, dose-ranging	- Dupilumab, 200 mg/4 weeks - Dupilumab, 300 mg/4 weeks - Dupilumab, 200 mg/2 weeks - Dupilumab, 300 mg/2 weeks (all SUBQ)	776	40 weeks	- Patients 18 years of age or older with asthma diagnosis for 12 months or more - Current treatment with medium-to-high dose ICSs plus a LABA with a stable dose for one month or greater before screening - Pre-baseline FEV1 of 40% to 80%, reversibility of 12% or greater - 200 mL in FEV1 after the administration 200 ug to 400 ug salbutamol at screening - ACQ-5 score at or greater than 1.5 at screening and baseline visit	- Greater than 1 severe exacerbation in the 24-week treatment period - Adjusted AER - Change in FEV1 from baseline to Week 12, L, LS mean (SE) - Change in Fev1 from baseline to Week 24, L, LS mean (SE) - Change in FEV1 from baseline to Week 24, L, LS mean (SE)	- Change in ACQ-5 score from baseline to Week 24, S mean (SE) - Change in AQLQ score from baseline to week 24, LS mean (SE) - Change in AM asthma symptom score from baseline to week 24 - Change in PM asthma symptom score from baseline to week 24, LS mean (SE) - Change in FeNO form baseline to Week 24, LS mean (SE)

Efficacy/Effectiveness

	Placebo	Dupixent® 200mg q4w	Dupixent®, 300mg q4w	Dupixent®, 200mg q2w	Dupixent®, 300mg q2w
N (%)	N=158	N=154	N=157	N=150	N=157
Change in ACQ-5	-1.14 (0.08)	-1.32 (0.08)	-1.34 (0.08)	-1.49 (0.08)	-1/45 (0.08)

Serious Adverse Events

Patients with, n (%)	Placebo	Combined Dupixent®
	N=158	N=611
Any TEAE	18 (75)	483 (79)
Any	9 (6)	45 (7)

score from baseline					
Change in AQLQ score from baseline	0.88 (0.09)	1.12 (0.09)	1.18 (0.08)	1.20 (0.09)	1.24 (0.08)
Change in AM asthma symptom score from baseline to Week 24	-0.36 (0.05)	-0.53) (0.05)	-0.54 (0.05)	-0.57 (0.05)	-0.56 (0.05)
Change in PM asthma symptom score from baseline to week 24	-0.39 (0.06)	-0.52 (0.06)	-0.59 (0.06)	-0.60 (0.06)	-0.61 (0.06)
Change in FeNO from baseline to Week 24	10.91 (5.39)	-5.47 (5.75)	-16.61 (5.55)	-21/86 (5.59)	-29.39 (5.44)

treatment-emergent SAE		
Any TEAE leading to treatment discontinuation	5 (3)	27 (4)
Any TEAE leading to death	0	2 (less than 1)
URTI (greater than 5% of patients)	28 (18)	83 (14)
Injection site erythema (greater than 5% of patients)	12 (8)	79 (13)
Headache	20 (13)	62 (10)
Nasopharyngitis	15 (9)	59 (10)
Bronchitis	16 (10)	51 (8)
Influenza	5 (3)	38 (6)
Sinusitis	11 (7)	36 (6)
URTI (greater than 10% of patients)	56 (35)	216 (35)
Injection site reaction (greater than 10% of patients)	21 (13)	110 (18)
Bacterial infections	3 (2)	5 (1)
Herpes viral infections	1 (1)	3 (less than 1)

Weaknesses Impacting Internal/External Validity

- Short duration of the study in patients with uncontrolled persistent asthma
- Small number of patients per dose regimen
- Only q2w dosing was evaluated into Phase III
- Approved treatment options remain limited

Reference: Rathinam KK, Abraham JJ, Vijayakumar TM. Dupilumab in the Treatment of Moderate to Severe Asthma: An Evidence-Based Review. *Curr Ther Res Clin Exp*. 2019 Oct 15;91:45–51.						
Study Design and Evidence Grade	**Drug Regimens**	**N**	**Time Horizon**	**Databases searched**	**Endpoints**	
					Primary	**Secondary**
MA, Systematic search				PubMed Cochrane library Embase ClinicalTrials.gov		
Efficacy/Effectiveness					**Serious Adverse Events**	
Efficacy and safety profile of dupilumab in the treatment of moderate-to-severe asthma Addition of dupilumab to conventional therapy improves FEV1 and reduces risk of severe asthma exacerbations in patients. Using dupilumab with LABAs used with inhaled corticosteroids improves clinical outcomes and quality of life in patients with moderate to severe asthma.					**Weaknesses Impacting Internal/External Validity** ● Still in emerging stage of acceptance ● Ongoing studies needed to determine dupilumab's long-term efficacy and safety for future extensive use	

Abbreviations used in this table: AC =active control, CCS = case-control study, DB = double blind, PC = placebo control, PCS = prospective cohort study, PG = parallel group, MA = meta-analysis MC = multicenter, RCS = retrospective cohort study, RCT = randomized controlled trial, XO = crossover.

Cost-Effectiveness Evidence Summary

<table>
<tr><th>Ref. and Sponsor</th><th>QHES Score</th><th>Study Design and Treatments Compared</th><th>Time Horizon and Demographics</th><th>Model Inputs and Data Sources</th><th>Results:
Base Case, Sensitivity Analysis and Limitations</th></tr>
<tr><td>1. Budget Impact Model (BIM) of Dupixent® against Current Treatment Mix</td><td>100</td><td>ICER model using the potential population for Dupixent® (approximately 237,000 patients per year)

Comparing Dupixent® to current treatment mix (27% on biologics and 73% on SoC)

Biggest competitor of Dupixent® is Xolair® (74.9% of biologics)</td><td>Time: 5 year analysis

Demographics: 1.2 million patients over 5 years or approximately 237,000 per year with moderate to severe asthma</td><td>- Population data from census and CDC prevalence data in 2016
- Market share based on IQVIA US Defined Daily Doses for July 2018
- 2017 National Population Projections Datasets
- Treatment costs</td><td>Base Case: Per Patient Budget Impact Calculation Over 5 Years

<table><tr><td colspan="6">Average Annual Per Patient Budget Impact</td></tr><tr><td></td><td>WAC</td><td>Net Price</td><td>$150,000/ QALY</td><td>$100,000/ QALY</td><td>$50,000/Q ALY</td></tr><tr><td>Dupilumab</td><td>$46,059</td><td>$38,912</td><td>$22,127</td><td>$17,945</td><td>$13,764</td></tr><tr><td>Current Treatment Mix</td><td colspan="5">$44,651</td></tr><tr><td>Difference (Dupilumab - Current Treatment Mix)</td><td>$1,408</td><td>($5,738)</td><td>($22,524)</td><td>($26,705)</td><td>($30,887)</td></tr></table>
Sensitivity Analysis: One-way sensitivity analysis on current and future drug prices.

Limitations: Refer to the Markov model below (#2), which was the same model used to determine cost-effectiveness analysis.</td></tr>
<tr><td>2. Long-Term Cost Effectiveness</td><td>100</td><td>Markov model based on models formerly developed for Xolair® and Nucala®

Comparing 5 biologic therapies for lifetime cost-effectiveness based on QALY</td><td>Time: Lifelong horizon

Demographics: Mean age = 46, 62% female, 17% chronic OCS users</td><td>- Average life expectancy
- NICE reports
- FDA labeled population
- Manufacturer net price data</td><td>Base Case: Incremental Cost-Effectiveness Ratio and Annual Price

<table><tr><td></td><td>Incremental Cost-Effectiveness Ratio</td><td>Annual Price</td></tr><tr><td>Omalizumab</td><td>$325,000</td><td>$28,900</td></tr><tr><td>Mepolizumab</td><td>$344,000</td><td>$29,500</td></tr><tr><td>Reslizumab</td><td>$391,000</td><td>$28,900</td></tr><tr><td>Benralizumab</td><td>$371,000</td><td>$27,800</td></tr><tr><td>Dupilumab</td><td>$351,000</td><td>$31,000</td></tr></table>
Sensitivity Analysis: One-way sensitivity analysis. Given Willingness to pay, non-exacerbation utility improvement, exacerbation reductions, and chronic oral steroid reduction.

Limitations: No long run clinical evidence on biologic treatment responders or discontinuation rate, further research is suggested. Lack of clinical evidence for subpopulations with income or ethnic disparities</td></tr>
<tr><td colspan="6">Abbreviations used in this table: LYS = life-years saved, QALY = quality-adjusted life-year, QOL = quality of life.</td></tr>
</table>

Background

Disease Background

Chronic inflammation of the airway, unregulated expiratory airflow and a multitude of symptoms, such as shortness of breath and coughing, are just a few of the characteristics that often accompany asthma. It is estimated that asthma affects 23 million Americans. In adolescence, there are higher rates of the disease in males, but an alteration occurs into adulthood where females have a higher prevalence. 11.6% of those with asthma are African American, followed by 8.3 % of white non-hispanics. Risk factors include genetics, weight, sex, allergans and air pollution, among others.[1]

Disease Burden

On average, the US economy spends nearly $80 million annually on asthma according to a study conducted from 2008-2013. The study projected that more than 15 million Americans had asthma. More recent estimates are up to 23 million affected by the disease, which would increase this economic projection. The social aspects of the disease are taxing. Symptoms can be difficult to control, and exacerbations can get in the way of daily tasks, such as work or school, leading to a diminished quality of life. Sleeping through the night can also prove difficult. Asthma can deter adolescents from playing sports even though oftentimes exercise can help with symptoms. In some cases, having asthma can prevent one from joining the military. Traveling to places with high altitudes or humidity can make breathing difficult.[15]

Pathophysiology

Type 2 inflammation occurs due to a specific type of CD4+ T-cells (Th2). Typically, type-2 asthma is triggered by allergens, bacteria and viruses. When an allergan comes into contact with a dendritic cell, it differentiates into a Th2 cell through the aid of IL-4. This newly formed Th2 cell, in turn, then stimulates the release of more IL-4, IL-5 and IL-13. These three IL are called type2-associated cytokines because they drive the inflammatory response. IL-4 triggers B-cells to make IgE, which causes mast cells to secrete inflammatory mediators such as histamine, and recruit eosinophils to sites of tissue injury. IL-13 has the same capabilities as IL-4, in addition to mucus production, smooth muscle contractility and collagen deposition. IL-5 primarily acts on eosinophil migration and maturation.[17,18] Through all of these changes, the airway tries to compensate through bronchoconstriction and mucus plugging of the inflamed airway.[1]

Treatment Alternatives

There are pharmacologic options for the treatment of asthma in multiple dosage forms. Inhaled medications are often more advantageous because they can go directly to the lungs at higher concentrations. Many devices for this type of drug delivery exist. Nonpharmacologic treatments include finding triggers and avoiding them when possible.[16]

Preferred Existing Therapy

Inhaled corticosteroids are the most effective treatment for asthma. This drug class suppress cytokines and inflammatory mediators. When the use of an inhaled corticosteroid is not enough to control asthma, the

addition of a LABA or omalizumab may be necessary to improve lung function. LABAs are not recommended for monotherapy because they cannot control exacerbations.[16]

Other Therapeutic Alternatives

Oral systemic corticosteroids may be used if the asthma is difficult to control or severe. There is some hesitation in this being first-line therapy due to a large number of side effects possible. Immunotherapy is an option for those that have ineffective medication therapy and suffer from symptoms all year round. Cromolyn sodium is another alternative treatment used before exercise or exposure to a known trigger. Leukotriene modifiers are an adjunct therapy to LABA, but only show modest improvement.[16]

Product Background

Pharmacology

Dupixent® is a human monoclonal IgG4 antibody that inhibits the IL-4 and IL-13 signaling mechanism. In doing so, proinflammatory cytokines and IgE cannot be released. It accomplishes this by binding to the IL-4Rα subunit.[14]

Pharmacokinetics[12]

Route of administration	Subcutaneous injection
Bioavailability	61% to 64%
Time to peak	Approximately 1 week
Plasma half-life	There is limited human data on half-life
Route(s) of elimination	Monoclonal antibodies do not undergo significant renal elimination. It is possible that Dupixent® is eliminated in two ways. It is hypothesized that at high concentrations, a proteolytic pathway is used. At low concentrations, saturable and a non-linear pathway is used.

Methodology

Dupixent® compared to IL-5 antibodies as maintenance add-on treatment for moderate-to-severe asthma with eosinophilic phenotype or OCS dependent asthma from 2017.

Databases Searched

Academic Search Complete including PubMed, Medline, International Pharmaceutical Abstracts, CINAHL, ProQuest

Secondary Sources

Icer-Review.org
Lexicomp

Search Strategy

Dupixent®, dupilumab, asthma, monoclonal antibodies, eosinophilic asthma

Inclusion Criteria

RCT, Meta-analyses, systematic reviews, control intervention studies

Search Results

Study Type	N	Published	Unpublished
Randomized controlled trials (RCT)	34	X	
Meta-analyses of RCTs	5	X	
Systematic reviews	7	X	
Cost-utility modeling studies	1	X	
Budget impact modeling studies	1	X	
Control intervention studies	6	X	
Other (not peer-reviewed)	1	X	

Articles Excluded from Evidence Synthesis

Reason for Exclusion	N
Study was not randomized	1

References

1. Dupixent. Sanofi and Regeneron Pharmaceuticals, Inc. edossier AMCP P&T Competition.https://www.amcpfoundation.org/student-pharmacists/amcp-foundation-annual-pt-competition/2020-p-t-competition. 2019.
2. Tice JA, Walsh JME, Synnott P, et al. Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. Boston, Institute for Clinical and Economic Review, 2018.
3. Dupixent.https://www.dupixent.com/?&utm_source=google&utm_medium=cpc&utm_campaign=Brand_Agnostic_General_Exact&utm_term=dupixent+manufacturer&gclid=Cj0KCQiAsbrxBRDpARIsAAnnz_OGVrTZXUYmXpAuv8XC3vkE1lpEVQYSzj33Vo2DMh5Ur_uJQgdlgLwaAj4dEALw_wcB&gclsrc=aw.ds. 2019. Accessed January 22, 2020.
4. Xolair. https://www.xolair.com/?cid=xol_PS_MIXLCUWB0056_11&c=MIXLCUWB0056. 2020. Accessed January 22, 2020.
5. Cinqair. https://www.cinqair.com/?utm_source=google&utm_medium=cpc&utm_campaign=USA_GO_SEM_B_BM_Cinqair-DTC-General&utm_term=cinqair+drug&utm_content=Treatment&gclid=Cj0KCQiAsbrxBRDpARIsAAnnz_Njmud5HCGTqVM1Vz1j_cQzWQZ9SEz3Up8sNK2-ZHkf_IoquYfVcVYaAildEALw_wcB&gclsrc=aw.ds 2018. Accessed January 22, 2020.
6. Fasenra. https://www.fasenrahcp.com/ 2019. Accessed January 22, 2020.
7. Nucala. https://www.nucala.com/?cc=ps_GKW31IYBL674952&mcm=20013&gclid=Cj0KCQiAsbrxBRDpARIsAAnnz_PZHfTOCZ6NaS6WJHh64KuA4nxh_IMBiW2ER3MUeu_KOUXP1orIM4AaAifJEALw_wcB&gclsrc=aw.ds 2019. Accessed January 22, 2020.
8. Ramonell R, Iftikhar I. Effect of anti-IL5, anti-IL-R, anti-IL13 therapy on asthma exacerbations: a network meta-analysis. *Lung* [Internet]. 2020 Jan 1. Available from: https://doi.org/10.1007/s00408-019-00310-8
9. Iftikhar I, Schimmel M, Bender W, Swenson C, Amrol D. Comparative efficacy of anti-IL4, IL-5 and IL-13 drugs for the treatment of eosinophilic asthma: a network meta-analysis. *Lung*. 2018 Oct;196(5):517-530.
10. Wenzel S, Ford L, Pearlman D, Spector NS, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013;368(26):2455–66.
11. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet Respir Med*. 2016 Jul 2;388(10039):31–44.
12. Corren JN, Castro MM, Chanez Pundefined, Fabbri Lundefined, Joish Vundefined, Amin Nundefined, et al. Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. *Eur Ann Allergy Clin Immunol*. 2019;122(1):41–9.
13. Korn et. al. Dupilumab improved asthma control in patients with controlled, moderate-to-severe asthma, regardless of exacerbations in the previous year. Poster or Paper presented at: 60th Congress of the German Respiratory Society; March 13-16, 2019; Munich, Germany.
14. Dupilumab. (Lexi-DrugsTM). Lexi-Comp, Inc.; Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Accessed January 9, 2020.
15. Nurmagambetov T, Kuwahara R, Garbe P. The Economic Burden of Asthma in the United States, 2008–2013. *Ann Am Thorac Soc*. 2018; 15(3): 348-356. doi:10.1513/annalsats.201703-259oc.

16. Guidelines for the diagnosis and management of asthma (EPR-3). National Institutes of Health, NHLBI 2007 Asthma Guidelines. https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma. 2007. Accessed December 14, 2019.
17. Reineke T. Dupixent®: another contender prepares to enter the asthma arena. *Managed Care Magazine*. 2018 Sep 3. https://www.managedcaremag.com/archives/2018/9/dupixent-another-contender-prepares-enter-asthma-arena. 2019. Accessed January 4, 2020.
18. Carr T, Zeki A, Kraft M. Eosinophilic and noneosinophilic asthma. *Am J Resp Crit Care Med*. 2018 Jan 1;197(1):22-37.