PharmaNote®

Vol. 33, Issue 2 November 2017 Established 1985

Dupilumab (Dupixent®): A Novel Agent for Atopic Dermatitis

Anita Patel, PharmD Candidate

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory skin disease that is often characterized by pruritus and recurrent lesions of the skin. Commonly beginning during infancy, it affects approximately 10 to 20% of children and up to 3% of adults. AD may be caused by cutaneous hyperreactivity to environmental triggers, skin barrier dysfunction, or immunologic triggers (i.e., food and inhalant allergens, microbial infection, or autoantigens). This is generally a result of increased transepidermal water loss and permeation to allergens, irritants, and microbes. Clinical manifestations of the disease include skin dryness, erythema (reddening of the skin), oozing, and crusting. It is typically associated with elevated serum levels of immunoglobulin (Ig) E, which is an antibody found in the lungs, skin, and mucous membranes. IgE mediates mast cell proliferation, and in turn releases histamine and cytokines during the inflammatory response.[1-4]

The most commonly used treatments for mild forms of AD are topical corticosteroids and emollients. Topical calcineurin inhibitors are an alternative to topical corticosteroids and are generally used around the facial area due to their poor penetration into the skin, making it ideal for sensitive areas. For moderate to severe forms of the disease, ultraviolet light therapy or oral cyclosporine are treatment options to consider after topical therapy.[1] In March 2017, a new agent, dupilumab (Dupixent®), was granted approval by the US Food and Drug Administration for the treatment of moderate to severe forms of AD that is not well controlled by the use of topical therapies. The purpose of this article is to review the pharmacology, clinical trials, adverse effects, dosing and administration, precautions, and costs of dupilumab in the treatment of AD.

IN THIS ISSUE

Pharmacology

Dupilumab is an interleukin (IL)-4 receptor antagonist. It is a fully human monoclonal IgG4 antibody that binds to the alpha subunit of the IL-4 receptor. This binding inhibits the subsequent signaling of IL-4 and IL-13 cytokines (Th2 cytokines), which drive the inflammatory response mechanism of atopic diseases such as asthma and AD. With administration of dupilumab, serum levels of IL-4 and IL-13 are increased, leading to an effective inflammatory response against these diseases.[5] Moreover, these cytokines contribute directly to barrier dysfunction by acting on keratinocyte differentiation and barrier protein, lipids, and production of antimicrobial peptides.[4]

Dupilumab has been shown to follow nonlinear target-mediated pharmacokinetics. After a dose increase from 75 mg to 600 mg (8-fold increase), the systemic exposure increased by 30-fold.[4] It is administered subcutaneously and in clinical trials it has been shown to reach peak plasma concentrations (Cmax) ± standard deviation (SD) of 70.1 ± 24.1 mcg/mL by approximately 1 week following the initial subcutaneous dose of 600 mg. The bioavailability after a subcutaneous dose is estimated to be 64% and the mean volume of distribution ± SD is approximately 4.8 ± 1.3 L. The metabolism of dupilumab has not yet been clearly established, but similar to endogenous IgG, it is suspected to be degraded into small peptides and amino acids via catabolism. In clinical trials, steady-state concentrations were achieved by week 16. The median times to non-detectable concentration (<78 ng/mL) were 10 and 13 weeks after the last steady-state dose of dupilumab 300 mg was administered every 2 weeks or once every week, respectively. Dupilumab has not yet been studied in patients with hepatic or renal impairment, or in the pediatric population. However, in patients aged 65 and older, dose adjustments are not necessary. In obese patients, trough concentrations were shown to be lower than those with normal body weight.[6]

Table 1 | Pharmacokinetics of dupilumab[6]

Absorption	
C_{max} (SubQ)	1 week
C_{ss}	16 weeks
Bioavailability	~64%
Distribution	
V_d	~4.8 ± 1.3 L
Metabolism	Degradation into peptides and amino acids
Elimination	Unknown

C_{max} = maximum concentration; **C_{ss}**= concentration at steady state; **L** = liter; **SubQ** = subcutaneous

Clinical Trials

Early-Phase Trials

A series of four early-phase clinical trials were first conducted to evaluate the safety of dupilumab (**Table 2**). All four of these studies were randomized, double-blind, and placebo-controlled. Two of the trials (Study M4A and Study M4B) were 4 weeks of dose-escalated dupilumab monotherapy. The third trial, Study M12, was 12 weeks of dupilumab monotherapy, and lastly, the fourth trial, Study C4, was dupilumab in combination with topical glucocorticoids for 4 weeks. Trial endpoints were generally assessed by an improvement in the Eczema Area and Severity Index (EASI) score, the Investigator's Global Assessment (IGA) score, and/or pruritus reduction based on a numerical rating scale. The EASI scores range from 0 to 72, with higher numbers indicating greater severity. A favorable IGA score is rated as either 0 (clear) or 1 (almost clear) with regard to the eczema.[7]

Studies M4A and M4B were phase 1 studies which included adults with moderate to severe forms of AD that was not well-controlled with topical glucocorticoids. Study M4A was conducted in the U.S. and randomly assigned patients to receive placebo (6 patients) or dupilumab at a dose of 75 mg (8 patients), 150 mg (8 patients), or 300 mg (8 patients) with all therapies administered subcutaneously once weekly.[7] The multinational study, Study M4B, was conducted in a similar fashion to M4A except 10 patients received placebo, and dupilumab was given at a dose of 150 mg (14 patients) or 300 mg (13 patients) once weekly. The results of studies M4A and M4B indicated a dose-dependent increase in the proportion of patients who had a 50% improvement in the EASI score at day 29, and a reduction in pruritus over time.[7]

Study M12, a phase 1 trial, was a randomized, placebo-controlled trial consisting of patients with moderate to severe AD who were given dupilumab monotherapy (weekly subcutaneous dose of 300 mg) with the primary endpoint being efficacy and secondary endpoint being safety. This trial was comprised of 109 patients who were randomly assigned dupilumab (55 patients) or placebo (54 patients). In this study, 85% of patients receiving dupilumab had a 50% reduction in EASI score compared to only 35% of patients who received placebo. Moreover, 40% of patients in the dupilumab group compared to 7% of patients in the placebo group scored 0-1 on the IGA scale. Lastly, pruritus scores decreased greater in the dupilumab group (by 55.7%) compared to the placebo group (by 15.1%).[7]

Study C4, a phase 2a trial, was the last in the series and was a 4-week combination therapy of dupilumab with topical glucocorticoids compared to placebo plus topical glucocorticoids. This trial was a randomized, double-blind, placebo-controlled trial, where twenty-one patients were given dupilumab at a weekly dose of 300 mg and ten patients were given placebo. Both treatment groups also received a standardized regimen of topical glucocorticoids. The endpoints measured in this trial were EASI score reduction and reduction in pruritus on the numerical-rating scale. By study end, 100% of the dupilumab group compared to 50% of the placebo group ($p = 0.002$) met EASI-50 (reduction of ≥50% in EASI score). The pruritus reduction score also showed sustained reduction with the combination of dupilumab plus topical glucocorticoids, compared with placebo plus topical glucocorticoids ($p = 0.005$).[7] Findings from this trial suggest that a combination of dupilumab plus topical glucocorticoid therapy is more effective than topical glucocorticoids alone in reducing eczema area and severity, as well as reducing pruritus.

Phase 2b Trial

A phase 2b trial was conducted to evaluate the efficacy and safety of dupilumab. This was a randomized, placebo-controlled, dose-ranging trial from 91 study centers all over the world. It enrolled patients with an EASI score of ≥12 at screening (≥16 at baseline), who had an inadequate response to topical therapy or for whom topical therapy was not recommended. Patients were randomized to receive either dupilumab 300 mg once a week, 300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks, 100 mg every 4 weeks, or placebo once a week. All treatments were administered subcutaneously for 16 weeks. The primary outcome was efficacy based on EASI score least-squares mean percentage change from baseline to week 16. At week 16, all dupilumab groups showed improvement in EASI scores compared with placebo ($p< 0.0001$ for all pairwise comparisons). Pruritus numerical rating scale scores also showed significant improvement in the dupilumab groups when compared with placebo at week 16 ($p< 0.0001$ for all pairwise comparisons).[8] From this trial, the findings suggest that dupilumab given in a dose-dependent manner results in improvements from baseline in the severity of AD and in pruritus.

SOLO 1 and SOLO 2

The SOLO 1 and SOLO 2 trials were two recent randomized, double-blind, placebo-controlled phase 3 studies (**Table 2**). These two trials were identical in design to provide replication of results and included adults with moderate to severe forms of AD inadequately controlled by topical therapy. Patients were randomly assigned to receive dupilumab 300 mg subcutaneously weekly, dupilumab 300 mg subcutaneously every other week alternating with placebo, or placebo weekly for a total of 16 weeks. The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the IGA and a reduction of ≥2 points in that score from baseline to week 16. The secondary endpoint was the proportion of patients who had at least 75% improvement in EASI scores (EASI-75). In SOLO 1, the primary outcome was achieved in 38% of patients receiving dupilumab every other week and in 37% of patients receiving dupilumab weekly, compared to 10% in the placebo group ($p <0.001$ for both comparisons with placebo). SOLO 2 had similar results with the primary outcome occurring in 36% receiving dupilumab every other week and in 36% receiving dupilumab weekly, compared to 8%in the placebo group ($p <0.001$ for both comparisons with placebo). Other noted favorable outcomes included reduction in pruritus and symptoms of anxiety or depression and an overall improvement in quality of life which was assessed by the Dermatology Life Quality Index (DLQI) questionnaire scores. It was concluded that the results from these two trials further support the findings from the earlier-phase studies in that dupilumab is a safe and effective agent in the treatment of moderate to severe forms of AD.[5]

LIBERTY AD CHRONOS

The latest phase 3 trial, LIBERTY AD CHRONOS, was a 1-year, randomized, double-blinded, placebo-controlled study (**Table 2**). This study was aimed to evaluate dupilumab's long-term efficacy and safety in adults with moderate-to-severe AD who had inadequate response to topical corticosteroids. Patients were randomly assigned to receive dupilumab 300 mg once weekly, dupilumab 300 mg every 2 weeks, or placebo every week. Patients given dupilumab every 2 weeks received matching placebo during the weeks when dupilumab was not given. All three groups

Table 2 | Summary of clinical trials for dupilumab

Trial	Design	Treatments	Primary Endpoint	Results
Study M4A (2014)	Phase I, randomized, double-blind, placebo-controlled	• Dupilumab 75 mg SC once weekly (n= 8) • Dupilumab 150 mg SC once weekly (n= 8) • Dupilumab 300 mg SC once weekly (n= 8) • Placebo once weekly (n= 6)	≥EASI-50, IGA score of 0 or 1, and pruritus reduction on numerical-rating scale score at week 4	4-week monotherapy: • ≥EASI-50: placebo= 19%; dupilumab= 59% • IGA: placebo= 6%; dupilumab= 12% • Change in pruritus score: placebo= -18.6±12.1; dupilumab= -41.3±4.3
Study M4B (2014)	Phase I, randomized, double-blind, placebo-controlled	• Dupilumab 150 mg SC once weekly (n= 14) • Dupilumab 300 mg SC once weekly (n= 13) • Placebo once weekly (n= 10)	≥EASI-50, IGA score of 0 or 1, and pruritus reduction on numerical-rating scale score at week 4	4-week monotherapy: • ≥EASI-50: placebo= 19%; dupilumab= 59% • IGA: placebo= 6%; dupilumab= 12% • Change in pruritus score: placebo= -18.6±12.1; dupilumab= -41.3±4.3
Study M12 (2014)	Phase I, randomized, double-blind, placebo-controlled	• Dupilumab 300 mg SC once weekly (n= 55) • Placebo once weekly (n= 54)	≥EASI-50, IGA score of 0 or 1, and pruritus reduction on numerical-rating scale score at week 12	12-week monotherapy: • ≥EASI-50: placebo= 20%; dupilumab= 69% • IGA: placebo= 4%; dupilumab= 18% • Change in pruritus score: placebo= -11.2±5.4; dupilumab= -44.5±3.9
Study C4 (2014)	Phase IIa, randomized, double-blind, placebo-controlled	• Dupilumab 300 mg SC once weekly + topical glucocorticoid (n= 21) • Placebo once weekly + topical glucocorticoid (n= 10)	≥EASI-50, IGA score of 0 or 1, and pruritus reduction on numerical-rating scale score at week 4	4-week combination therapy: • ≥EASI-50: placebo= 50%; dupilumab= 100% • IGA: placebo= 30%; dupilumab= 52% • Change in pruritus score: placebo= -24.7±15; dupilumab= -70.7±4.7
Thaçi, et al. (2015)	Phase IIb, randomized, placebo-controlled, dose-ranging	• Dupilumab 300 mg SC once weekly (n= 63) • Dupilumab 300 mg SC every 2 weeks (n= 64) • Dupilumab 200 mg SC every 2 weeks (n= 61) • Dupilumab 300 mg SC every 4 weeks (n= 65) • Dupilumab 100 mg SC every 4 weeks (n= 65) • Placebo once a week (n= 61)	EASI score reduction at week 16	EASI score (mean baseline → week 16): • Dupilumab 300 mg SC once weekly: 30.1 → 7.2 • Dupilumab 300 mg SC every 2 weeks: 33.8 → 10.7 • Dupilumab 200 mg SC every 2 weeks: 32.9 → 10.9 • Dupilumab 300 mg SC every 4 weeks: 29.4 → 9.8 • Dupilumab 100 mg SC every 4 weeks: 32.2 → 17.4 • Placebo once a week: 32.9 → 25.6

Thaçi, et al. (2015)	Phase IIb, randomized, placebo-controlled, dose-ranging	• Dupilumab 300 mg SC once weekly (n= 63) • Dupilumab 300 mg SC every 2 weeks (n= 64) • Dupilumab 200 mg SC every 2 weeks (n= 61) • Dupilumab 300 mg SC every 4 weeks (n= 65) • Dupilumab 100 mg SC every 4 weeks (n= 65) • Placebo once a week (n= 61)	EASI score reduction at week 16	EASI score (mean baseline → week 16): • Dupilumab 300 mg SC once weekly: 30.1 → 7.2 • Dupilumab 300 mg SC every 2 weeks: 33.8 → 10.7 • Dupilumab 200 mg SC every 2 weeks: 32.9 → 10.9 • Dupilumab 300 mg SC every 4 weeks: 29.4 → 9.8 • Dupilumab 100 mg SC every 4 weeks: 32.2 → 17.4 • Placebo once a week: 32.9 → 25.6
SOLO 1 (2016)	Phase III, randomized, double-blind, placebo-controlled	• Dupilumab 300 mg SC once weekly (n= 223) • Placebo once weekly (n= 224) • Dupilumab 300 mg SC every other week alternating with placebo (n= 224)	IGA score 0/1 and ≥2 point reduction at week 16	IGA (week 16): • Dupilumab 300 mg SC once weekly: 37% • Dupilumab 300 mg SC every other week: 38% • Placebo: 10%
SOLO 2 (2016)	Phase III, randomized, double-blind, placebo-controlled	• Dupilumab 300 mg SC once weekly (n= 239) • Placebo once weekly (n= 236) • Dupilumab 300 mg SC every other week alternating with placebo (n= 233)	IGA score 0/1 and ≥2 point reduction at week 16	IGA (week 16): • Dupilumab 300 mg SC once weekly: 36% • Dupilumab 300 mg SC every other week: 36% • Placebo: 8%
LIBERTY AD CHRONOS (2017)	Phase III, randomized, double-blind, placebo-controlled	• Dupilumab 300 mg SC once weekly plus TCS (n= 270) • Dupilumab 300 mg SC every 2 weeks plus TCS (n= 89) • Placebo once weekly plus TCS (n= 264)	IGA score 0/1 and ≥2 point reduction and EASI-75 at week 52	IGA (week 52): • Dupilumab once weekly: 40% • Dupilumab every 2 weeks: 36% • Placebo: 13% EASI-75 (week 52): • Dupilumab once weekly: 64% • Dupilumab every 2 weeks: 65% • Placebo: 22%

SC = subcutaneous; **mg =** milligram; **n =** number of patients; **CS =** topical corticosteroid
EASI-50 = 50% improvement on the Eczema Area and Severity Index, ranges from 0 to 72 with higher numbers indicating greater severity
EASI-75 = 75% improvement on the Eczema Area and Severity Index, ranges from 0 to 72 with higher numbers indicating greater severity
IGA = Investigator's Global Assessment score, a favorable IGA score is 0 (clear) or 1 (almost clear), percentages represents percentage of patients that achieved a score of 0 or 1

Table 3 | Averse effects of dupliumab in phase 3 clinical trials[5]

Adverse Reactions	SOLO 1 and SOLO 2			LIBERTY AD CHRONOS		
	Placebo (n=456)	Dupilumab every other week (n-465)	Dupilumab every week (n=455)	Placebo (n=315)	Dupilumab every other week (n=110)	Dupilumab every week (n=315)
Injection-site reaction	6%	11%	16%	8%	15%	19%
Conjunctivitis	1%	5%	4%	8%	14%	19%
URTI	2%	3%	5%	10%	10%	14%
Non-skin infection[a]	23%	28%	29%	58%	57%	53%

a: nasopharyngitis, sinusitis, etc…; **URTI =** upper respiratory tract infection

received concomitant topical corticosteroids with or without topical calcineurin inhibitors, which were used in body areas considered inadvisable for topical corticosteroids (i.e. sensitive areas such as the face). These concomitant topical agents could be stopped, tapered, or restarted as clinically required throughout the study. Endpoints of this trial included the proportion of patients achieving IGA 0/1 (clear/almost clear; 0-4 scale) and ≥2 point reduction from baseline at week 52, and the proportion of patients achieving 75% improvement in EASI (EASI-75) from baseline to week 52. At week 52, 40% of patients receiving dupilumab once weekly and 36% of patients receiving dupilumab every 2 weeks achieved an IGA score of 0/1 and ≥2 point improvement on the IGA scale, compared to 13% of patients who received placebo ($p < 0.0001$, each treatment group vs placebo). Additionally, 64% in the dupilumab once weekly group and 65% in the dupilumab every 2 weeks group achieved an EASI-75 response at week 52, compared to 22% in the placebo group ($p < 0.0001$, each treatment group vs placebo).[9] As the first long-term trial, the efficacy of dupilumab is sustained throughout one year, indicating the long-term benefits of this agent when added to topical corticosteroids.

Adverse Effects

The most frequently occurring adverse events identified in the SOLO 1, SOLO 2, and LIBERTY AD CHRONOS trials were injection-site reactions and conjunctivitis, with incidences being similar and significantly higher between the treatment groups compared to the placebo group. Upper respiratory tract infections and non-skin infections occurred at similar rates in the dupilumab groups compared to placebo.[5] Table 3 summarizes the incidence of these various adverse events that occurred in the phase 3 trials.

Dosing and Administration

The initial dose of dupilumab is 600 mg subcutaneous (divided as two 300 mg injections at different sites) once, followed by a maintenance dose of 300 mg subcutaneous every other week. If a dose is missed, it is appropriate to administer the dose within 7 days of the missed dose. If more than 7 days have elapsed, patients should forgo the missed dose and administer the next dose at the regular schedule. Laboratory monitoring for dupilumab is not necessary, other than monitoring for reduction in pruritus. Clinically significant effects of the agent can be seen in as little as 4 weeks but the majority of patients had improved outcomes at 16 weeks. Dupilumab comes in prefilled syringes and should be stored in the refrigerator at 2-8°C (36-46°F); it may also be stored at room temperature for a maximum of 14 days. When administering, it should be removed from the refrigerator and allowed to reach room temperature, which usually takes about 45 minutes, before injecting.[6] Injection sites should be rotated with each dose to prevent injection-site reactions, such as pain, erythema, or skin blistering. It is important to note that excess preparation should be discarded as the syringe is recommended for single-use only.

Precautions and Drug Interactions

Dupilumab is contraindicated in patients who have a hypersensitivity to the drug or any of its excipients. The medication should be discontinued if a hypersensitivity reaction develops during treatment. Insufficient evidence exists for its use in asthma patients; however, patients should be advised to consult their healthcare provider before adjusting or discontinuing their asthma therapy. There is also not enough evidence of dupilumab's use in pregnancy and lactation; therefore, the risks and benefits need to be taken into consideration.[6]

Concurrent administration of dupilumab with live vaccines should be avoided due to possible increased risk of infection. Therefore, it is generally recommended to update all immunizations before initiating dupilumab therapy. Since dupilumab is an antagonist of the IL-4 receptor, altered formation of CYP450 enzymes can also occur due to increased levels of inflammatory cytokines such as IL-4.[6] Consequently, drugs that are CYP450 substrates (i.e., warfarin, cyclosporine, carbamazepine, digoxin, tacrolimus) should be monitored or dose-adjusted if dupilumab is initiated.[6]

Cost

Dupilumab is a specialty medication, and its cost can be relatively expensive. One prefilled syringe (300 mg/2 mL) typically costs approximately $1707.70 (average wholesale price). Unfortunately, dupilumab is not on the Medicare or Medicaid formulary at this time. However, the manufacturer of dupilumab has a DUPIXENT MyWayTM program, which offers a $0 copay card to eligible patients with commercial health insurance.

Summary

Dupilumab is a new injectable treatment for moderate to severe forms of AD. It has been approved for added-on therapy in patients whose symptoms are inadequately controlled with topical corticosteroids or when those therapies are contraindicated. It is a human monoclonal antibody that antagonizes the IL-4 receptor, preventing the inflammatory release of cytokines, chemo-

kines, and IgE, all of which are proinflammatory mediators that play a critical role in the development of AD. Dupilumab is initially dosed at 600 mg subcutaneously once, followed by 300 mg subcutaneously every other week for maintenance therapy. Improvements in signs and symptoms of AD, such as reduction in pruritus, generally occur in 16 weeks. The most common adverse reactions reported in dupilumab-treated patients are injection-site reactions and conjunctivitis. The high cost of this medication may be a barrier for majority of patients; however, a cost-savings program through the manufacturer is available for eligible patients. The results from clinical trials showed that dupilumab was both efficacious and safe in moderate-to-severe forms of AD in adults, with sustained benefits even during long-term treatment. However, lack of studies in pediatric patients limits the use of dupilumab in this specific population, where AD is most commonly observed.

References

1. Leung, DY. New insights into atopic dermatitis. Journal of Clinical Investigation. 2004;113(7):1070-1070. doi:10.1172/jci200421060c.
2. Weidinger S, Novak N. Atopic dermatitis. The Lancet. 2016;387(10023):1109-1122. doi:10.1016/s0140-6736(15)00149-x.
3. Liu F-T, Goodarzi H, Chen H-Y. IgE, Mast Cells, and Eosinophils in Atopic Dermatitis. Clinical Reviews in Allergy & Immunology. 2011;41(3):298-310. doi:10.1007/s12016-011-8252-4.
4. Derme AM, Romanelli M, Chiricozzi A. Spotlight on dupilumab in the treatment of atopic dermatitis: design, development, and potential place in therapy. Drug Design, Development and Therapy. 2017;Volume 11:1473-1480. doi:10.2147/dddt.s113192.
5. 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(24):2335-2348. doi:10.1056/nejmoa1610020.
6. Dupixent® injection [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2017 Mar.
7. Beck, LA, Thaçi D, Hamilton JD, et al. Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis. New England Journal of Medicine. 2014;371(2):130-139. doi:10.1056/nejmoa1314768.
8. Thaçi, D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. The Lancet. 2016;387(10013):40-52. doi:10.1016/s0140-6736(15)00388-8.
9. Blauvelt A, Bruin-Weller MD, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. The Lancet. 2017;389(10086):2287-2303. doi:10.1016/s0140-6736(17)31191-1.

Editor's Corner

Canagliflozin (Invokana®) Boxed Warning Update

The FDA has recently updated the safety labeling for canagliflozin (Invokana®) to include a boxed warning for increased risk of leg and foot amputations. The increased risk was found and published in the FDA mandated cardiovascular and renal safety studies for canagliflozin, CANVAS and CANVAS-R.[1] In the trials, a total of 10,142 patients with type 2 diabetes were randomly assigned to canagliflozin or placebo treatment over a mean duration of 3 years. The risk of amputation was 5.9-7.5 out of every 1,000 patients treated with canagliflozin compared to 2.8-4.2 out of every 1,000 patients treated with placebo. The most common amputations were of the toe and middle of the foot.

Currently, there are three sodium-glucose cotransporter-2 inhibitors on the market: empagliflozin, canagliflozin, and dapagliflozin. Empagliflozin and canagflizosin have completed FDA mandated cardiovascular and renal safety trials, and both have demonstrated reduction in cardiovascular events in patients with elevated cardiovascular risk.[1,2] Results of the ongoing cardiovascular study for dapagliflozin, DECLARE, have yet to be published.[3] Of the SGLT-2 inhibitors, at this time only canagliflozin carries the boxed warning for increased risk of below the knee amputation.

References:

1. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine. 2017, Jun 12.
2. Zinman, B, Wanner, C, Lachin, Jet, et al. 2015. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015, 373(22): 2117-2128.
3. https://clinicaltrials.gov/ct2/show/NCT01730534. Web accessed 10/30/17.

PharmaNote®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University *of* Florida