HIGHLIGHTS FROM AMCP NEXUS 2019

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# Table of Contents

Analyzing Treatment Patterns in Non-Small Cell Lung Cancer Patients Receiving Chemotherapy or Immuno-Oncology  
Health Care Costs Associated with Uterine Fibroids and Heavy Menstrual Bleeding  
Eversense Continuous Glucose Monitoring System Reported Effective  

### Science and Innovation Theater:
- How Access Decisions are Increasingly Influenced by an Evolving Policy Landscape  
- A Review of Social Determinants of Health, Associated Challenges, and Potential Solutions  
- Prevention, Treatment, and Cost-Minimization in Alzheimer’s Disease Care  
- An Analysis of Atopic Dermatitis Patients Prior to Monoclonal Antibody Treatment  

Synchronized Medication Refills Improve Outcomes in Patients with Diabetes  
Analyzing the Cost-Effectiveness of a New Primary Open-Angle Glaucoma Treatment  
The Importance of Value-Based Services and How They Are Best Managed  
An Analysis of Treatment Patterns and Outcomes in Patients with Triple Negative Breast Cancer  

- Study Finds New Drug Effective in Managing Atopic Dermatitis  
- The Importance of Value-Based Services and How They Are Best Managed  
- An Analysis of Treatment Patterns and Outcomes in Patients with Triple Negative Breast Cancer  
- An Overview of Digital Therapeutics (DTx) and Relevant Regulation  
- A Health Care Reform Update: The ACA, Trump Administration’s Impact, and Public Perception  
- Approaches to Value-Based Contracting with Clinical Strategies  
- Science and Innovation Theater: A Biosimilar Oncology Therapy for Patients: Totality of Evidence
Analyzing Treatment Patterns in Non-Small Cell Lung Cancer Patients Receiving Chemotherapy or Immuno-Oncology

Researchers presenting at AMCP Nexus 2019 recently conducted a retrospective observational study to assess patient profiles and treatment patterns among advanced non-small cell lung cancer (aNSCLC) cases. Among the study’s key findings was a high utilization of first-line systemic chemotherapy in treating aNSCLC and an increasing incidence of immuno-oncology (IO) use within this patient population in recent years.

The treatment of aNSCLC has been significantly changed with the introduction of IO therapies. These drugs have shown optimistic outcomes and toxicity effects in clinical trials, but there is limited information regarding their treatment patterns and sequencing in U.S. community oncology environments since the emergence of IO treatments. To address this discrepancy, the study researchers analyzed data from aNSCLC patients who initiated first-line treatment with the U.S. Oncology Network (USON).

The authors for this retrospective study analyzed data regarding adult aNSCLC patients who underwent first-line treatment with systemic chemotherapy, an IO regimen, or a targeted therapy. These patients received such therapies between March 2015 and August 2018 and were followed up until February 2019. Patient data were obtained from electronic health records, with baseline characteristics and treatment patterns being assessed through description.

A total of 7,746 patients were eligible for the study, with an average age of 68 years (range, 26-90+ years; 55.0% male; 78.9% white) at the start of first-line therapy. Of those, 5,859 (75.6%) patients received systemic chemotherapy, 907 (11.7%) IO monotherapy, 656 (8.5%) TT, and 324 (4.2%) IO combination therapies as a first-line treatment. Of the patients with squamous cell carcinoma, 86.8% underwent systemic chemotherapy, 12.7% IO therapy, and only 0.6% for targeted therapy. Of the non-squamous cell carcinoma patients, 70.8% received systemic chemotherapy, 17.7% IO therapy, and 11.5% targeted therapy.

After first-line treatment, 46.7% went on to receive second-line therapy and 15.9% to a third. In the second quarter of 2015, which was the first complete quarter of the study period, the second quarter of 2018, 36.0% of first-line therapies contained an IO therapy (22.9% monotherapy and 13.1% combination therapy).

The most common sequences observed were first-line chemo followed by second-line IO (n=2,127 [27.5%]) therapy and first-line chemotherapy followed by second-line chemotherapy (n=636 [8.2%]). Otherwise, 14.2% (n=175) of the 1,231 patients who received first-line IO therapy went on to receive second-line chemotherapy, 4.0% (n=49) to IO, 2.4% (n=30) to targeted therapy, and 79.4% (n=977) did not proceed to receive further treatment during the study.

“Current treatment patterns show high utilization of 1L chemo for aNSCLC over the study period. Adoption of IO therapy is increasing, however, <40% of 1L pts treated in the U.S. community oncology setting received an IO regimen in the second quarter of 2018. Future studies should investigate outcomes associated with choice of 1L regimen and continue to evaluate the need for effective and safe IO options,” the authors concluded.

This research was sponsored by Pfizer and EMD Serono.

Health Care Costs Associated with Uterine Fibroids and Heavy Menstrual Bleeding

Total Health Care costs are significantly higher in women with both uterine fibroids (UFs) and heavy menstrual bleeding (HMB) as opposed to those with only one of these conditions, according to new research to be presented at AMCP Nexus 2019.

Among female patients with symptomatic UF, HMB is one of the most prevalent burdens they face, according to the study abstract. Citing a lack of existing research regarding the economic burden these women with HMB or UF face, these study researchers aimed to compare the health care costs of women with both conditions to those of patients with UF only, HMB only, or neither.

This retrospective cohort study leveraged Truven MarketScan Commercial Claims and Encounters Database information collected from July 2007 to June 2018. Women
between ages 18 and 51 were placed in four cohorts based on diagnoses of HMB only (ICD-9-CM 626.2 or 627.0, or ICD-10-CM N92.0, N92.1 or N92.4), UF only (ICD-9 218.x or ICD-10 D25.x), UF and HMB, and controls with neither condition. Baseline characteristics and treatment types (medication, surgical or procedure, or no treatment) in the year after initial diagnosis were evaluated for each group. Multivariable analyses controlling for age, region, type of insurance, total health care costs at baseline, and the Charlson Comorbidity Index were used to compare all-cause health care costs (inpatient and outpatient visits, surgeries, ER visits, and pharmacy) in the year after diagnosis between the UF and HMB cohort and the other groups. Multivariable analyses controlling for age, region, type of insurance, total health care costs at baseline, and the Charlson Comorbidity Index were used to compare all-cause health care costs (inpatient and outpatient visits, surgeries, ER visits, and pharmacy) in the year after diagnosis between the UF and HMB cohort and the other groups.

A total of 1,149,007 women with UF and/or HMB and 2,244,368 controls were included in this study. 54.1% of those diagnosed with UF also received HMB diagnoses, and 31.3% of those diagnosed with HMB were also diagnosed with UF. In the 12 months post-diagnosis, 33.4% of those with both UF and HMB received no treatment, 25.3% underwent surgery or a procedure without medication use, 15.5% received medication only, and 25.7% underwent surgery/procedure and received medication. The average all-cause total health care costs in the group with both UF and HMB ($17,505 [$27,642]) were significantly greater than those of the women with UF only ($14,803 [$32,097]), HMB only ($10,522 [$24,912]), or the controls with neither symptom ($5,880 [$19,708]; all P<0.05).

“Among women diagnosed with both UF and HMB, mean all-cause total health care costs were significantly higher than for women with UF only, HMB only, and controls,” the authors of the study concluded.

This research was sponsored by AbbVie.


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**Eversense Continuous Glucose Monitoring System Reported Effective**

**RESEARCH TO BE** presented at AMCP Nexus 2019 suggests that the Eversense Continuous Glucose Monitoring (CGM) System is an effective tool for managing patients with diabetes. This Eversense CGM was approved by the FDA in June 2018 for use in patients aged 18 years or older with diabetes. The system uses a 90-day implanted sensor that leverages fluorescent technology and demonstrated its accuracy (MARD 8.5%) and safety in three trials. To evaluate the real-world experience and performance of this CGM system, researchers analyzed data from 205 patients who completed a full 90-day sensor wear period using the device.

Patient sensor glucose (SG) data from August 2018 to May 2019 were assessed using the Eversense Diabetes Management System (DMS). The SG average, coefficient of variation (%CV), standard deviation (SD), glucose measurement index (GMI; a mathematical estimate of the HbA1c), and percent and time at various SG ranges, were all calculated. The accuracy of the sensor was analyzed using paired SG and self-monitored blood glucose (SMBG) measurements for calibrations that were done twice daily. The researchers also assessed the sensor reinsertion rate 120 days after the initial insertion date and the median wear time of the transmitter in patients with data beyond 30 days after the insertion.

A total of 205 patients were recruited (110 male, 94 female, 1 unreported). Of these, 129 participants identified as type 1 diabetics, 18 as type 2 diabetics, and 58 as unreported. A total of 50 of the patients reported not having experience with CGM, 112 had prior experience with the technology, and 43 were unreported. According to the study abstract, SG, SD, %CV, and GMI were found to be 161.8 mg/dL (57.4 mg/dL), 0.35 (0.06), and 7.18% (0.80), respectively. The percentage of time spent in ranges below 54 mg/dL was 1.2% (18.0 min/day); between 54 and 70 mg/dL, 2.9% (41.8 min/day); between 70 and 180 mg/dL, 62.3% (897.7 min/day); between 181 and 250 mg/dL, 21.9% (315.8 min/day); and more than 250 mg/dL (severe hyperglycemia), 11.6% (166.7 min/day).

MARD (SD; 27,708 SG-SMBG paired points) was found to be 11.2% (11.3%), the sensor reinsertion rate was 76.9%, and the median time of transmitter wear was 83.6% in participants with a minimum of 30 days of data (92% of the entire population).

“Real-world data from the first 205 patients in the U.S. who completed a 90-day sensor wear period showed promising glycemic results,” the authors concluded in their study. “These data suggest that the implanted Eversense CGM system is a valuable tool for management of diabetes.”

This work was sponsored by Senseonics.

How Access Decisions are Increasingly Influenced by an Evolving Policy Landscape

A recent osteoporosis case study demonstrated that predictive cost modeling can be implemented in conjunction with reimbursement policies to determine the efficacy of screenings and therapies that stand to both achieve cost savings and preserve patient health. Researchers presented this case study in a Science and Innovation Theater at AMCP Nexus 2019.

The presenters noted that as the U.S. faces a growing aging population, the looming healthcare burden along with the associated costs can appear unsustainable, resulting in untenable decision-making by having to decide between therapeutic efficacy and cost effectiveness.

Osteoporosis doesn’t receive as much attention as other chronic diseases, the presenters noted, even though under-treated and undiagnosed cases of osteoporosis are creating a potential crisis in patient care. Approximately 200 million women worldwide are living with this disease, but fewer than 1 in 5 receive a diagnosis. Alarmingly, fewer than 1 in 3 women receive treatment, even after a fracture—and among those who are treated—less than 50% are adherent to treatment protocol beyond six months.

These fractures, according to the presentation, come at a high price. Given that dual x-ray absorptiometry (DXA) reimbursement has been reduced, with only an 11% usage rate (along with a 9% treatment rate), the effects of osteoporosis would incur costs of almost 2 trillion dollars by 2040. To mitigate this cost crisis, the researchers proposed that a 20% increase in DXA combined with 20% increase in treatment would result in savings of over $54 billion by 2040.

Some states and programs, the presenters noted, are now augmenting DXA screening rates and implementing fracture liaison services (FLS). Overall, lives of osteoporotic patients can only be improved with a multi-stakeholder effort. This three-tier initiative should include: government (which should devise statues ensuring DXA coverage while increasing Medicare DXA reimbursement and promoting disease awareness programs); providers, who should strive to inform and engage payers while leveraging care coordination; and the payers, who must create wellness benefit, and develop case management while also establishing policies for early disease identification.

Synchronized Medication Refills Improve Outcomes in Patients with Diabetes

New study results suggest that synchronized medication refills could potentially improve health outcomes in patients with diabetes.

Patients with diabetes, who frequently present with several comorbidities, often require complicated treatment regimens that make adherence difficult. Medication synchronization (the process of standardizing complex medication refill schedules) presents as a potential mechanism to both improve adherence rates and cut health care costs. To better understand the effect of these synchronized drug refill schedules on those suffering from diabetes, the present study authors assessed the relationship between medication synchronization and adherence, health care resource usage, and health care expenditures in patient with diabetes. The results of the study are to be presented at AMCP Nexus 2019.

The retrospective, cohort study evaluated the differences in diabetes medication adherence, inpatient admissions, and the total health care costs between patients using medication synchronization and propensity-score matched controls. These data were extracted from the 2015-2018 Truven MarketScan Research Databases, from which the subjects eligible for inclusion in the Pharmacy Quality Alliance (PQA) diabetes medication (excluding insulin) adherence measure were identified. Patients using two or more diabetes, statin, or renin-angiotensin system antagonist drug classes were included in this study.

Conditional logistic regression was leveraged to analyze the correlation between medication adherence and synchronization and generalized linear mixed models with log link and gamma distribution (expenditures) or negative binomial distribution (utilization) were used to evaluate economic outcomes. Odds ratios (OR), rate ratios (RR), and cost ratios (CR) were estimated from the data as well.

A total of 20,325 medication synchronization cases successfully met inclusion criteria and were matched to controls. The researchers found that commercial cases (n=16,136) had greater adherence (67.7% vs. 57.4% [OR=1.67; 95% CI, 1.59 to 1.75]), fewer hospital admissions (RR=0.59; 95% CI, 0.53 to 0.67), and lower median health care expenditures ($3,687 vs. $7,480 [CR=0.61; 95% CI=0.57 to 0.65]) than their matched control. It was also found that Medicare supplemental cases (n=4,189) had greater adherence (86.5% vs. 70.4% [OR=2.96; 95% CI, 2.62 to 3.35]), fewer hospital admissions (RR=0.72; 95% CI 0.63 to 0.82), and lower median health care expenditures ($7,353 vs. $10,592 [CR=0.69; 95% CI, 0.64 to 0.75]) than the controls as well.

Continued on page 34
Osteoporotic fractures can impact your plan as much as myocardial infarctions

Learn how you can help more members with postmenopausal osteoporosis at high risk for fracture by visiting ProliaPayerResources.com or contact your Amgen Account Manager

Indications
Prolia® is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia® reduces the incidence of vertebral, nonvertebral, and hip fractures.

Important Safety Information
• Contraindications: Prolia® is contraindicated in patients with hypersensitivity. Pre-existing osteonecrosis of the jaw must be corrected prior to initiating Prolia®. Prolia® is contraindicated in women who are pregnant and may cause fetal harm. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia®. Prolia® is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions may include anaphylaxis, facial swelling and urticaria.
• Same Active Ingredient: Prolia® contains the same active ingredient (denosumab) found in XGEVA®. Patients receiving Prolia® should not receive XGEVA®.
• Hypersensitivity: Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia®. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Prolia®.
• Hypocalcemia: Hypocalcemia may worsen with the use of Prolia®, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, including treatment with other calcium-lowering drugs, clinical monitoring of calcium and mineral levels is highly recommended within 14 days of Prolia® injection. Concomitant use of calcimimetic drugs may worsen hypocalcemia risk and serum calcium should be closely monitored. Adequately supplement all patients with calcium and vitamin D.
• Osteonecrosis of the Jaw (ONJ): ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia®. An oral exam should be performed by the prescriber prior to initiation of Prolia®. A dental examination with appropriate preventive dentistry is recommended prior to treatment in patients with risk factors for ONJ such as invasive dental procedures, history of cancer, concomitant therapies (e.g. chemotherapy, corticosteroids, angiogenesis inhibitors), poor oral hygiene and concurrent disorders. Good oral hygiene practices should be maintained during treatment with Prolia®. The risk of ONJ may increase with duration of exposure to Prolia®.
For patients undergoing invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or oral surgeon. Extreme dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia® should be considered, based on individual benefit-risk assessment.
• Atypical Femoral Fractures: Atypical low-energy, or low trauma fractures of the shaft have been reported in patients receiving Prolia®. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with Prolia®. During Prolia® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be evaluated to rule out an incomplete femur fracture. Interruption of Prolia® therapy should be considered, pending a risk/benefit assessment, on an individual basis.
• Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia® Treatments: Following discontinuation of Prolia® treatment, fracture risk increases, including the risk of multiple vertebral fractures. New vertebral fractures occurred as early as 7 months on average 19 months after the last dose of Prolia®. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia® discontinuation. Evaluate an individual’s benefit/risk before initiating treatment with Prolia®. If Prolia® treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.
• Serious Infections: In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia® group than in the placebo group. Serious skin infections, as well as infections of the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia®. Endocarditis was also reported more frequently in Prolia®-treated patients. The incidence of opportunistic infections and the overall incidence of infections were similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.
Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia®, prescribers should assess the need for continued Prolia® therapy.
• Dermatologic Adverse Reactions: Epidermal and dermal adverse events such as dermatitis, eczema and ashes occurred at a significantly higher rate with Prolia® compared to placebo. Most of these events were not specific to the injection site. Consider discontinuing Prolia® if severe symptoms develop.
• Musculoskeletal Pain: Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with Prolia®. Consider discontinuing use if severe symptoms develop.
• Suppression of Bone Turnover: Pancreatitis has been reported with Prolia®. Consider discontinuing use if severe symptoms develop.
• Osteoporosis treatment post-fracture 1,‡

<table>
<thead>
<tr>
<th>Total osteoporotic fractures</th>
<th>Myocardial infarctions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual hospitalization costs</td>
<td>$5.1B</td>
</tr>
<tr>
<td>Hospitalization admission rate</td>
<td>45%</td>
</tr>
<tr>
<td>Intervention rate</td>
<td>17%</td>
</tr>
</tbody>
</table>

References:

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BRIEF SUMMARY OF PRESCRIPTION INFORMATION
Prolia (denosumab) injection, for subcutaneous use
Please see package insert for full prescribing information

INDICATION AND USAGE
Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, non-vertebral, and hip fractures.

CONTRAINDICATIONS
Hypocalcemia
Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia.

Pregnancy
Prolia may cause fetal harm when administered to a pregnant woman. In women of reproductive potential, pregnancy testing should be performed prior to initiating treatment with Prolia.

Hypersensitivity
Prolia is contraindicated in patients with a history of systemic hypersensitivity to any component of the product. Reactions have included anaphylaxis, facial swelling, and urticaria.

WARNINGS AND PRECAUTIONS
Drug Products with Same Active Ingredient
Prolia contains the same active ingredient (denosumab) found in Xgeva. Patients receiving Prolia should not receive Aegera.

Hypocalcemia
Clinically significant hypocalcemia including anaphylaxis has been reported with Prolia. Symptoms include hypotension, dyspnea, throat tightness, facial, and upper airway edema, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue further use of Prolia.

Hypocalcemia and Mineral Metabolism
Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia.

In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hyperparathyroidism, thyroid surgery, parathyroidectomy, hypovitaminosis D or calcium deficiency, hypocalcemic tetany, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis, treatment with other calcium-lowering drugs), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended within 14 days of Prolia injection. In some postmarketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis. These patients may also develop marked elevations of serum parathyroid hormone (PTH). Concomitant use of calcimimetic drugs may worsen hypocalcemia risk and serum calcium should be closely monitored. Instruct all patients with severe renal impairment, including those receiving dialysis, about the symptoms of hypocalcemia and the importance of maintaining calcium levels with adequate calcium and vitamin D supplementation.

Adequately supplement all patients with calcium and vitamin D. If Prolia is interrupted, consider transitioning to an alternative antiresorptive therapy.

Serious Infections
In a clinical trial of over 7000 women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the Prolia group than in the placebo group. Severe skin infections, as well as infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with Prolia. Eczematitis was also reported more frequently in Prolia-treated patients. The incidence of opportunistic infections was similar between placebo and Prolia groups, and the overall incidence of infections was similar between the treatment groups.

Advising patients to seek prompt medical attention if they develop signs or symptoms of serious infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired renal function are more likely to develop serious infections.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures
Atypical low energy or low trauma fractures of the shaft have been reported in patients receiving Prolia. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar region and are transverse or short oblique in orientation, without evidence of comminution. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-osteoporotic agents.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral, and many patients report prodromal pain in the affected area, usually presenting as aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contratuberal limb. Interruption of Prolia therapy should be considered, pending a benefit-risk assessment, on an individual basis.

Multiple Vertebral Fractures (MFV) Following Discontinuation of Prolia Treatment
Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. Cessation of Prolia treatment results in markers of bone resorption increasing above pretreatment values then returning to pretreatment values 24 months after the last dose of Prolia. In addition, bone mineral density returns to pretreatment values within 18 months after the last injection.

New vertebral fractures occurred as early as 7 months (on average 19 months) after the last dose of Prolia. Prior vertebral fracture was a predictor of multiple vertebral fractures after Prolia discontinuation. Evaluate an individual’s benefit-risk profile before initiating treatment with Prolia. If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy.

Musculoskeletal Pain
In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking Prolia. The time to onset of symptoms varied from one day to several months after starting Prolia. Consider discontinuing use if severe symptoms develop.

Suppression of Bone Turnover
In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

ADVERSE REACTIONS
The following severe adverse reactions are discussed below and also listed elsewhere in the labeling:

• Hypocalcemia
• Serious Infections
• Dermatologic Adverse Reactions
• Osteonecrosis of the Jaw
• Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Multiple Vertebral Fractures (MFV) Following Discontinuation of Prolia Treatment
The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis.

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Treatment of Postmenopausal Women with Osteoporosis
The safety of Prolia in the treatment of postmenopausal osteoporosis was assessed in a 3-year, randomized, double-blind, placebo-controlled, multinational study of 7088 postmenopausal women aged 60 to 91 years. A total of 3876 women were exposed to placebo and 3882 women were exposed to Prolia administered subcutaneously once every 6 months as a single 60 mg dose. All women were instructed to take at least 1 mg of calcium and 400 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 2.3% (n = 91) in the placebo group and 1.9% (n = 70) in the Prolia group. The incidence of nonfatal serious adverse events was 2.2% in the placebo group and 2.5% in the Prolia group. The percentage of patients who withdrew from the study due to adverse events was 2.1% and 2.4% for the placebo and Prolia groups, respectively.

Adverse reactions reported in a ≥ 2% of postmenopausal women with osteoporosis and more frequently than in placebo-treated women are shown in the table below.

Table 1. Adverse Reactions Occurring in ≥ 2% of Patients with Osteoporosis and More frequently than in Placebo-treated Patients

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Prolia</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>(N=386)</td>
<td>(N=387)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>(N=72)</td>
<td>(N=72)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>(N=64)</td>
<td>(N=64)</td>
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<tr>
<td>General Disorders</td>
<td>(N=3)</td>
<td>(N=3)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>(N=3)</td>
<td>(N=3)</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>(N=3)</td>
<td>(N=3)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>(N=3)</td>
<td>(N=3)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>(N=3)</td>
<td>(N=3)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>(N=3)</td>
<td>(N=3)</td>
</tr>
</tbody>
</table>

BLOOD AND LYMPHATIC SYSTEM DISORDERS

• Anemia

CARDIAC DISORDERS

• Angina pectoris

GASTROINTESTINAL DISORDERS

• Abdominal pain

GENERAL DISORDERS AND ADMINISTRATION SITES CONDITIONS

• Edema peripheral

• Asthenia

INFECTIONS AND INFESTATIONS

• Cytosis

• Upper respiratory tract infection

• Pneumonia

• Pharyngitis

• Herpes zoster

METABOLISM AND NUTRITION DISORDERS

• Hypercholesterolemia

• MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS

• Back pain

• Pain in extremity

• Musculoskeletal pain

• Bone pain

• Myalgia

• Spinal osteoarthritus

NERVOUS SYSTEM DISORDERS

• Sciatica

• Insomnia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

• Rash

• Pruritus

Hypocalcemia
Decreases in serum calcium levels to less than 8.5 mg/dL at any visit were reported in 0.4% women in the placebo group and 1.7% women in the Prolia group. The nadir in serum calcium level occurs at approximately 10 days after Prolia dosing in subjects with normal renal function.
In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 subjects with varying degrees of renal function, serum calcium levels < 7.5 mg/dl or symptomatic hypocalcemia were observed in 5 subjects. Those included in the normal renal function group, 10% of subjects in the creatinine clearance 50 to 80 ml/min group, 29% of subjects in the creatinine clearance < 30 ml/min group, and 29% of subjects in the hemodialysis group. These subjects did not receive calcium and vitamin D supplementation. Osteonecrosis of the jaw was reported in 0.4% women in the placebo group and 1.7% women in the Prolia group. No patients in the placebo group had any sign of ONJ. In a study of patients treated with Prolia for up to 5 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies, as was assessed using a chemiluminescent cell-based in vitro biochemical assay. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with antibody development. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Risk Summary**

Prolia is contraindicated for use in pregnant women because it may cause harm to a fetus. There are insufficient data with denosumab use in women in pregnancy to inform any drug-associated risks for adverse developmental outcomes. *Osteoporosis* from exposure to cytomolgous monkeys dosed monthly with denosumab throughout pregnancy at a dose of 50-fold higher than the recommended human dose based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, and absent limb nodes, abnormal bone growth, and decreased neonatal growth.

**Data**

*Animal Data* The effects of denosumab on prenatral development have been studied in both cynomolgous monkeys and genetically engineered mice in which RANKL (ligand of RANKL) expression was turned off by gene removal (a “knockout mouse”). In cynomolgous monkeys doused subcutaneously with denosumab throughout pregnancy starting at gestational day 20 and at a pharmacologically active dose 50-fold higher than the recommended human dose based on body weight, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth; reduced bone strength; reduced hematopoiesis, dental dysplasia, and tooth malformation; and decreased neonatal growth. At birth to 1 month of age, infants had measurable blood levels of denosumab (122-1271 mg of maternal load). Following a recovery period from birth to 6 months of age, the effects on bone quality and strength returned to normal, there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and normal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no-obsorable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated. Mammary gland histopathology at 5 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated. In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation. The no effect dose for denosumab-induced teratogenesis is unknown. However, a C50 of 22.9 mg/kg was identified in cynomolgous monkeys as a level in which no biologic effects (NOEL) of denosumab were observed (no inhibition of RANKL).

**Lactation**

**Risk Summary**

There is no information regarding the presence of denosumab in human milk, the effects on the breastfed infant, or the effects on milk production. Denosumab was detected in the maternal milk of cynomolgous monkeys up to 1 month after the last dose of denosumab (0.55R ml serum ratio) and maternal mammary gland development was normal, with no impaired lactation. However, pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation.

**Females and Males of Reproductive Potential**

Based on findings in animals, Prolia can cause fetal harm when administered to a pregnant woman.

**Contraception**

Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Prolia.

**Males**

Denosumab was present at low concentrations (approximately 2% of serum exposure) in the seminal fluid of male subjects given Prolia. Following vaginal intercourse, the maximum amount of denosumab delivered to a female partner would result in exposures approximately 11000 times lower than the prescribed 60 mg subcutaneous dose, and at least 38 times lower than the NOEL in monkeys. Therefore, make condom use would not be necessary as it is unlikely that a female partner or fetus would be exposed to pharmacologically relevant concentrations of denosumab via seminal fluid.

**Pediatric Use**

Prolia is not recommended in pediatric patients younger than age 4 years because of the high rates of skeletal growth and the potential for Prolia to negatively affect long-bone growth and dentition. The safety and effectiveness of Prolia in pediatric patients have not been established.

Treatment with Prolia may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of Prolia therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≥ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 10 and 50 times (10 and 50 mg/kg dose higher than the recommended human dose of 60 mg administered every 6 months, based on body weight mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab. Cynomolgous monkeys exposed in utero to denosumab exhibited bone abnormalities, an absence of axillary, inguinal, mandibular, and mensoric lymph nodes, reduced hematopoiesis, tooth malformation, and decreased neonatal growth. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth.

**Geriatric Use**

Of the total number of patients in clinical studies of Prolia, 9143 patients (76%) were ≥ 65 years old, while 3576 (27%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**Renal Impairment**

No dose adjustment is necessary in patients with renal impairment. In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypercalcemia. Consider the benefit-risk profile when administering Prolia to patients with severe renal impairment or receiving dialysis. Clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.

**Hepatic Impairment**

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Prolia.

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.Prolia.com or call Amgen at 1-800-772-4436.

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1399
All rights reserved.
“Medication synchronization was associated with higher adherence, lower inpatient utilization, and lower health care costs,” the authors wrote. “Medication synchronization may facilitate improved health outcomes across various populations.”

This work was sponsored by Merck Sharp & Dohme.


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**Analyzing the Cost-Effectiveness of a New Primary Open-Angle Glaucoma Treatment**

**LATANOPROSTENE BUNOD OPHTHALMIC solution 0.024% (LBN; Vyzulta®)** may be an effective, cost-efficient alternative to commonly-used branded prostaglandin analog (PGA) therapies for glaucoma, according to new research presented at AMCP Nexus 2019.

Primary open-angle glaucoma (POAG) is a leading cause of visual disability and is predicted to increase in prevalence with the aging population. Causing visual impairment and incurring unwarranted medical costs, the condition can significantly reduce the quality of life in affected patients.

The primary goal of POAG treatments is to reduce the intraocular pressure (IOP) to limit the visual deficit that the patient encounters. PGAs are typically the first-line therapy for POAG, however, the large number of patients switching or stopping therapy or requiring adjunctive therapy makes adherence and persistence challenging to enforce.

LBN, a new IOP-lowering drug, introduced in 2017, has had success in lowering IOP with low rates of PGA-class associated side effects like hyperemia that often contribute to nonadherence. To compare the cost-effectiveness of LBN to that of branded topical PGAs for treating POAG, researchers used a decision-analytic model to estimate the clinical and health utility outcomes for each.

This model was developed using market-based distributions and weighted effectiveness, safety and cost estimates, over two years in three-month increments. Clinical input parameters in this study were taken from prescribing information and existing literature. Resource utilization estimates were obtained from treatment patterns in guidelines and published studies, and published estimates were used to assign health utilities to each health state. A US Medicare payer perspective was used, with costs (in $US 2018) and outcomes being discounted at 3% each year. The influence of key input parameters was examined using sensitivity analyses.

The researchers found that the total costs over 2 years in the base case were $6,168 for LBN and $6,619 for the aggregate PGA comparator. The mean quality-adjusted life years (QALYs) were found to be 1.60 and 1.58 for LBN and other PGAs, respectively, suggesting that LBN was more cost-efficient than PGAs, with higher utilities and lower costs. Including the costs of adjunctive therapy, drug costs for patients receiving LBN and PGAs were $4,176 and $4,150 and accounted for 68% and 63% of the total costs over two years, respectively.

Sensitivity analyses showed that LBN remained to be the more cost-efficient option when compared to each PGA, reducing the price of the aggregate PGA comparator, doubling the estimated use of adjunctive therapies, using commercial reimbursement rates, and assuming other cost discounting rates.

“Based on clinical trial data and indirect effectiveness comparisons, latanoprostene bunod 0.024% appears to be cost-saving compared to commonly-used branded PGA therapies for glaucoma over two years,” the authors concluded.

“Real world data should be gathered to update assumptions made in this model; however, these initial estimates suggest that small improvements in IOP control and reductions in hyperemia rates can have a meaningful impact on two-year glaucoma costs and health outcomes.”

This research was sponsored by Bausch Health LLC.


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**A Review of Social Determinants of Health, Associated Challenges, and Potential Solutions**

Researchers presenting at AMCP Nexus 2019 recently summarized some of the key social determinants of health and how they impact overall outcomes for patients with complex conditions such as cancer.

Social determinants of health were defined by the authors...
as follows: “The conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life. These forces and systems include economic policies and systems, development agendas, social norms, social policies, and political systems.”

One of the determinants addressed was access to healthy food and food insecurity. The authors noted that the average health care costs incurred by Ontario adults (18-64 years of age) over a 12-month span in relation to food insecurity status was $1,608, $2,161, $2,806, and $3,930 for those who are food secure, marginally food insecure, moderately food insecure, and severely food insecure, respectively. Barriers to this group include distance to supermarkets, transportation, and food deserts. Vulnerable populations typically include in low-income, rural, or minority communities, with discrimination being cited as a strong determinant within this population. The impacts of this poor nutrition are diabetes, obesity, CKD, high blood pressure, and cancer.

Access to health services and primary care was another social determinant addressed by the researchers, who noted that only 65% of adults under 65 have access to a primary care provider. These patients are less likely to receive preventative care therapies such as cancer and blood pressure screening, dental care, flu shots, and other vaccinations.

Housing quality was listed as a determinant in low-income families, with associated risks including lead poisoning, vector-borne diseases, and poor respiratory health due to mold from water leaks. The researchers also touched on health literacy as a social determinant of health, being that low health literacy is correlated with more frequent ER visits, increased hospitalizations, and poor medication adherence.

Many challenges exist when it comes to addressing these social determinants of health. The researchers listed fragmented data, the need for multifaceted interventions, barriers to language and culture, and education gaps as specific barriers to progress. They also discussed and proposed potential approaches to these issues, including targeted case management programs that leverage health risk assessments, collaborative holistic care teams, predictive analytics models that account for social determinants data, reimbursement services that aim to address social determinants, and partnerships with provider and community groups. Another innovative proposed solution involves digital cognitive behavioral therapy consisting of on-demand, web-based modular therapy programs. These platforms are created in academic institutions, backed by credible research, can be used independently or with clinical support, decrease the need for higher levels of care, and offer self-paced, convenient, HIPAA compliant solutions.


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**Prevention, Treatment, and Cost-Minimization in Alzheimer’s Disease Care**

**A COMPREHENSIVE PRESENTATION** on the diagnosis, treatment, and prevention of Alzheimer’s disease was recently given at AMCP Nexus 2019.

Regarding the emerging Alzheimer’s therapies, the authors noted that there are currently over 100 being tested in humans. These drugs include amyloid and tau protein modulating drugs and biologics, chemical messenger-based drugs, drugs emphasizing neuroprotection, and nutraceuticals.

They explained that amyloid plaques are character to the disease, noting that rare causes of familial Alzheimer’s all involve conflicts with amyloid processing. There is, however, a rare mutation that blocks the pathological amyloid cascade and prevents the disease according to the authors, presenting a potential target for treatments.

According to the authors, previous trials of amyloid-based therapies for Alzheimer’s disease include active and passive immunization, β-secretase and γ-secretase inhibitors (“BACE” inhibitors), and anti-aggregation therapies, however, these attempts have failed for various reasons. The authors also note that passive and active immunotherapies are at the center of ongoing studies targeting amyloid. They also noted that nutraceuticals are not regulated by the FDA and that unsubstantiated claims are common. Most of these treatments have failed when tested in Alzheimer’s patients, including ginkgo biloba, various vitamins, DHA, and other agents.

Notable developments in this research process included the SPRINT Memory and Cognition IN Decreased Hypertension (MIND) study, a randomized clinical trial comparing two strategies for managing hypertension. The two groups in this study are the intensive strategy group (systolic blood pressure goal < 120 mm Hg) and the standard care group (systolic blood pressure < 140 mm Hg). This work has found significant reductions in the risk of MCI and MCI/dementia in the intensive strategy group compared to the standard care group. It is the first trial to demonstrate a reduction in MCI incidence and MCI/dementia.

The researchers went on to address various value-based payment arrangements for early-stage Alzheimer’s disease treatments. Many drugs currently being researched are targeting
early-stage disease, with 7 phase III prevention trials and 26 phase III trials targeting MCI/mild stages are underway. There are also 99 drugs in phase II and III testing, with 74 being disease-modifying treatments that target disease pathology.

The team noted that treating dementia earlier would shift costs too much earlier in the patient’s disease progression. Preventative care was also discussed, with prevention trials aiming to minimize cognitive impairment in patients.


Study Finds New Drug Effective in Managing Atopic Dermatitis

AN INTERIM ANALYSIS of a real-world study of adults with atopic dermatitis (AD) presented at AMCP Nexus 2019 revealed that dupilumab correlates with increased treatment satisfaction and a sharp decline in concomitant AD therapies, specifically systemic corticosteroids (SCS).

The drug is currently approved for patients with moderate-to-severe AD not being properly managed by topical treatments. This approval applies only to patients 12 years or older in the US and adults in Europe. This study assessed change in treatment (Tx) satisfaction and concomitant AD therapies following dupilumab initiation from the EaRly REal WorLd Patient EValuation for dupilumab in Atopic Dermatitis (RELIEVE-AD) study, a prospective, longitudinal patient survey conducted in the US.

This new research assessed change in treatment satisfaction and concomitant treatments after the initiation of dupilumab treatment. The data were obtained from the patients enrolled in a prospective, longitudinal patient survey in the US called the EaRly REal WorLd Patient EValuation for dupilumab in Atopic Dermatitis (RELIEVE-AD) study. Patients who were invited to participate were adults with AD who had been prescribed dupilumab and were enrolled in its patient support program in the US.

Participants were surveyed at baseline prior to being given dupilumab, and again at one, two, three, six, nine, and 12 months follow-up. Baseline treatment was defined as the use of prescription topicals (corticosteroids, calcineurin inhibitors), PDE4 inhibitor, systemic corticosteroids, systemic immunosuppressants, or phototherapy in the past 4 weeks. This interim 6-month analysis (data-cut: Dec 6, 2018) included patient reported satisfaction with current treatments for AD and use of simultaneous AD treatments before and after dupilumab treatment had begun.

A total of 674 of the 1,010 patients responding to the baseline survey reported initiating dupilumab. The response rates of eligible patients were 89.8%, 89.1%, 84.2%, and 74.4% at months one, two, three, and six, respectively. The demographic and clinical findings at months 3 and 6 were comparable to those of the full sample. Those who reported to be very/extremely satisfied with their existing AD treatments increased from 2.9% at baseline to 57.8% at month one and 70.9% at month six (both P < 0.001).

Those who used concomitant AD treatments from three or more drug categories saw a reduction from 13.1% at baseline to 1.7% at month one and 1.5% at month six (both P < 0.001), and use from two different categories reduced from 34.3% to 14.7% and 12.1% at months one and six, respectively (both P < 0.001). The observed trends for treatments with individual drug categories were similar, with those for SCS decreasing by 73.5% by month six. The proportion of those with no concomitant AD therapy increased from the baseline 12.8% to 39.6% at month one and 41.3% at month six (both P < 0.001).

“While this dataset is still maturing, in this interim-analysis of a real-world study of adults with AD, dupilumab introduction corresponded with increased Tx satisfaction and rapid decline in concomitant AD therapies, especially SCS,” the authors concluded. “These data support the evidence demonstrating effectiveness of dupilumab for adults with moderate-to-severe AD.”

This research was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.


The Importance of Value-Based Services and How They Are Best Managed

VALUE-BASED STRATEGIES are designed to highlight how products fit in the disease state value continuum, showcase
products compared to other products, and identify key differentiators using real-world evidence, according to a new presentation at AMCP Nexus 2019. These strategies emphasize the overall disease state costs rather than the costs of medications.

Product value, according to the presenters, should be an integral part of product development and pipeline management throughout the product lifecycle. The presenters called for the incorporation of clinical value through the use of clinical studies, noting that required trials in development enhance product value assessment.

The researchers described the life cycle of value strategies to involve the evaluation of the landscape and pipeline, identification of gaps to build value, preparation for launch, and post-launch discovery. They add that product value should be strongly emphasized in the development phase.

Pre-launch work can aid in defining gaps in disease state. The use of real-world data evaluation of disease state results in the definition of potential place in therapy, assessment of competitor landscape and pipeline, and helps determine where trials should be focused, according to the presenters. Post-launch gap identification also leverages real-world evidence to determine areas where more research is needed, and also to compare real-world evidence to clinical trial outcomes.

The presenters described the launch preparation phase to include the following steps:

- Building knowledge of payers’ needs and values
- Assess what potential restrictions in the disease area or drug class
- Prepare accepted budget impact and cost-effectiveness thresholds
- Analyze and evaluate the expected market uptake and challenges
- Physician behavior and potential prescriber inertia
- Develop contracting strategy and risk-sharing agreements (VBC)

They went on to note that the payer should want to look at the evidence to build and evaluate the value story and review their utilization, trends, and disease history. If the payer has medical information, they look at the total disease cost of care and accepted budget impact and cost-effectiveness thresholds. Expected market uptake and challenges should also be considered. The payer should also develop restricted criteria for clinical reasons.

According to their presentation, they felt that risk-sharing agreements can replace traditional contracting or wrap with a traditional contract as well and added that some products may not be assessed in pre-launch. Post-marketing studies, real-world studies/registries, policies impacting coverage, additional evidence needs, and price reforms potentially impacting the disease area were suggested as possible solutions.


An Analysis of Treatment Patterns and Outcomes in Patients with Triple Negative Breast Cancer

A RECENT STUDY has found that duration and cost both increase as treatment lines progress in patients with metastatic triple negative breast cancer (TNBC). These study results were presented at AMCP Nexus 2019, and the research was also selected by the society as a Best Poster Abstract.

The researchers leveraged an oncology clinical data program integrated with claims data to describe treatment patterns and outcomes. The integration of clinical and claims data allows researchers to examine outcomes and characteristics that are not usually available in an individual database and is necessary for creating real-world evidence. The goal of using this data program was to evaluate treatment patterns, resource utilization, and total costs among TNBC patients.

Patients included in this study were those with metastatic TNBC diagnosed from February 2016 to May 2018 onwards with both clinical information from a Prior Authorization (PA) tool, based on NCCN guidelines, and claims from the Optum Research Database. Demographic data, treatment duration, resource utilization, total cost, and clinical information (such as HER2 status, hormone status, metastatic status, and treatment line) were collected and uploaded to a dynamic web-based Tableau® dashboard. Cost data were all adjusted to represent 2017 values.

The researchers identified 357 TNBC patients were identified, with 213 (60%) of them being in their first line of therapy and 48% being at least 55 years of age. The top five observed first line regimens, cyclophosphamide + doxorubicin, carboplatin/cisplatin + gemcitabine, paclitaxel, paclitaxel protein-bound, and carboplatin/cisplatin + paclitaxel, accounted for 76% of patients (accounting for 25%, 24%, 14%, 8%, and 5%, respectively.

The average first-line therapy duration was 76.2 days (median: 57 days) with 80% of all patients having non-censored first lines. 41 patients (19%) had at least one
inpatient stay during their first line. The average total cost of first line therapy was $50,087 (SD: $56,111).

A total of 144 patients were in line 2+ at the first encounter in the PA data, with the top three most common non-first line treatment therapies accounting for 49% of all episodes [carboplatin/cisplatin + gemcitabine (19%), eribulin mesylate (18%), and paclitaxel protein-bound (12%)]. Average 2+ line therapy duration was found to be 91.1 days with 118 (82%) being non-censored. 37 (26%) patients had 1+ inpatient stay during the line, and the average total cost of non-first line therapy was $56,310 (SD: $62,768).

“As the treatment lines progress, duration and costs increase by 20% and 12% respectively,” the study authors concluded. “Combination of clinical and claims based data points are valuable to evaluate treatment outcomes in specific personalized sub cohorts of patients and maybe one day used for treatment selection at individual lines of therapy.”


An Analysis of Atopic Dermatitis Patients Prior to Monoclonal Antibody Treatment

A NEW ANALYSIS of real-world data presented at AMCP Nexus 2019 suggests there exist significant unmet medical needs in patients with atopic dermatitis (AD) prior to their use of dupilumab.

The study researchers reported that most patients treated with dupilumab have moderate-to-severe AD, type 2 and other comorbidities, and significant prior usage of off-label systemic medications. Patients with moderate-to-severe AD experience significant burden from symptoms such as itchiness, poor quality of sleep, depression and anxiety, and type 2 inflammatory comorbidities (T2-IC). Dupilumab, a human monoclonal antibody treatment that targets the interleukin-4 receptor α, is approved for use in moderate-to-severe AD patients aged 12 and older in the U.S. The drug is approved in adults in the European Union and other countries.

Dupilumab has demonstrated efficacy and safety in improving AD signs and symptoms in multiple clinical trials, used both on its own and in concert with topical corticosteroids (TCS). In this new study, the researchers aimed to identify real-world patient characteristics and AD treatments before dupilumab treatment (pre-dup tx). The data used in this research were collected at point-of-care between March 2016 and November 2017 from Modernizing Medicine’s dermatology-specific (MMDS) EMR, which covers roughly 5,000 dermatologists in the U.S. To be included in this study, patients had to be at least 18 years of age, have one or more dupilumab prescription between the drug’s approval date (March 28, 2017) and November 20, 2017, (index date for all pts = 1st dupilumab Rx after U.S. approval), and at least one year of pre-index observation. Descriptive analyses were carried out for index AD symptoms and signs: (0-5-point Investigator Global Assessment [IGA] scale, percent body surface area [BSA] affected, 0-10-point Peak Pruritus Numerical Rating Scale [PNRS]), comorbidities, and pre-index tx.

A total of 4,253 patients were involved in this trial, with an average age of 46 years (±17.8) and 51% being female. The IGA levels in 1,488 patients were: 0/1 (clear): 4.8%; 2 (mild): 6.6%; 3 (moderate): 32.4%; 4 (marked): 46.3%; 5 (severe): 9.9%. The average BSA in 157 patients was found to be 39.3 (±27.4) with an average PNRS in 836 patients being 5.5 (±3.2).

The most common T2-IC were asthma (32.1%), allergic rhinitis (25.6%), and allergic urticaria (4.0%). Other prevalent comorbidities were anxiety (15.9%), depression (12.6%), and skin infections (16.8%). Pre-dup tx in 3,813 of the patients were TCS (78.2%), oral/injectable corticosteroids (44.9%), topical calcineurin inhibitors (23.5%), phosphodiesterase-4 inhibitors (22.4%), systemic immunosuppressants (18.8%) or phototherapy (6.7%). Two, three, or four different pre-dup tx forms were used by 37.5%, 10.1%, 0.5%, of 3,813 patients, respectively.

“These data indicate that most pts treated with dupilumab in the real world have moderate-to-severe AD, type 2 and other comorbidities, and significant prior off-label systemic medications use, suggesting a significant unmet medical need prior to the introduction of dupilumab,” the authors concluded.

This research was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

APPROVED FOR PATIENTS AGED 12 YEARS AND OLDER WITH UNCONTROLLED MODERATE-TO-SEVERE ATOPIC DERMATITIS

INDICATION
DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION: DUPIXENT is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis and serum sickness or serum sickness-like reactions, were reported in <1% of subjects who received DUPIXENT in clinical trials. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT.

Conjunctivitis and Keratitis: Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder in these patients. Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical or inhaled corticosteroids abruptly upon initiation with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Atopic Dermatitis Patients with Comorbid Asthma: Advise patients not to adjust or stop their asthma treatments without consultation with their physicians.
Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

IMPORTANT SAFETY INFORMATION

TRIAL DESIGNS: A total of 917 adult patients in Trials 1 and 2 (16-week trials), 251 adolescent patients in Trial 6 (16-week trial), and 421 adult patients in Trial 3 (52-week trial) with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription treatments were randomized to DUPIXENT or placebo. For all patients in Trial 3, lesions were treated with concomitant TCS. All adults received 300 mg Q2W following a 600 mg loading dose. Adolescents ≥60 kg also received this dose, while adolescents <60 kg received 200 mg Q2W following a 400 mg loading dose. Eligible patients had an IGA score ≥3 (overall atopic dermatitis lesion severity scale of 0 to 4), an EASI score ≥16 on a scale of 0 to 72, and body surface area involvement of ≥10%. At baseline, 52% of adults and 48% of adolescents had an IGA score of 3 (moderate atopic dermatitis), 48% of adults and 54% of adolescents had an IGA of 4 (severe atopic dermatitis), mean EASI score was 33 for adults and 36 for adolescents, and weekly averaged peak pruritus NRS was 7 on a scale of 0 to 10 for adults and 8 for adolescents.

TRIAL RESULTS: The primary endpoint was the change from baseline in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and ≥2-point improvement at Week 16 (38% and 36% of adults treated with DUPIXENT vs 10% and 9% with placebo in Trials 1 and 2, respectively, \(P<0.0001\); 24% of adolescents treated with DUPIXENT vs 2% with placebo in Trial 6, \(P<0.0001\); 39% of adults treated with DUPIXENT + TCS vs 12% with placebo + TCS in Trial 3, \(P<0.0001\)). Other endpoints included change from baseline in the proportion of subjects with EASI-75 at Week 16 (improvement of ≥75%; 51% and 44% of adults treated with DUPIXENT vs 15% and 12% with placebo in Trials 1 and 2, respectively, \(P<0.0001\); 42% of adolescents treated with DUPIXENT vs 8% with placebo in Trial 6, \(P<0.0001\); 69% of adults treated with DUPIXENT + TCS vs 23% with placebo + TCS in Trial 3, \(P<0.0001\)) and reduction in itch as defined by ≥4-point improvement in the Peak Pruritus NRS at Week 16 (41% and 36% of adults treated with DUPIXENT vs 12% and 10% with placebo in Trials 1 and 2, respectively, \(P<0.0001\); 37% of adolescents treated with DUPIXENT vs 5% with placebo in Trial 6, \(P<0.0001\); 59% of adults with DUPIXENT + TCS vs 20% with placebo + TCS in Trial 3, \(P<0.0001\)).

EASI, Eczema Area and Severity Index; IGA, Investigator’s Global Assessment; NRS, numerical rating scale; Q2W, once every 2 weeks; TCS, topical corticosteroids.

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS (cont’d)

Parasitic (Helminth) Infections: It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.
Parasitic (Helminth) Infections:
It is unknown if DUPIXENT will influence the immune response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS:
The most common adverse reactions (incidence ≥1% at Week 16) in adult patients with atopic dermatitis are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. The safety profile in adolescents through Week 16 was similar to that of adults with atopic dermatitis. In an open-label extension study, the long-term safety profile observed in adolescents through Week 52 was consistent with that seen in adults with atopic dermatitis.

DRUG INTERACTIONS:
Avoid use of live vaccines in patients treated with DUPIXENT.

USE IN SPECIFIC POPULATIONS
• Pregnancy: Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus.

• Lactation: There are no data on the presence of DUPIXENT in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

Please see brief summary of full Prescribing Information on the following pages.

Visit DupixentHCP.com/AtopicDermatitis to learn more
5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections. Treatment with pre-existing helminth infections before initiating therapy with DUPIXENT, if patients become infected while receiving treatment with DUPIXENT and do not respond to anthelminthic treatment, discontinues treatment with DUPIXENT until the infection resolves.

6. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:
- Hypersensitivity [see Warnings and Precautions (5.1)]
- Conjunctivitis and Keratitis [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were male, 67% were white, 24% were Asian, and 6% were black; in terms of comorbidity conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCSs). A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis. Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Week 16 vs 52 (Trials 1-4)

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups. Table 1 summarizes the most frequent adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 1: Adverse Reactions Occurring in ≥2% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT Monotherapy</th>
<th>DUPIXENT + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>51 (10)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>51 (10)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (1)</td>
<td>(1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>(1)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Pooled analysis of Trials 1, 2, and 4.
*Analysis of Trial 3 where subjects were on background TCS therapy.

DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

Adverse events were more frequently reported in DUPIXENT + TCS group than in the DUPIXENT monotherapy group and placebo group and were due to asthma or atopic dermatitis.

Eczema Herpeticum and Herpes Zoster

Herpes zoster or eczema herpeticum.

Adverse reactions were more frequent with DUPIXENT + TCS than placebo in moderate-to-severe atopic dermatitis subjects; all of these subjects recovered.
atopic dermatitis (Trial 7). The safety profile of DUXPENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUXPENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

**Asthma**

A total of 2868 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium- to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus add-on controller therapy were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 52% were white. DUXPENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively. In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUXPENT 200 mg Q2W group, and 6% of the DUXPENT 300 mg Q2W group.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUXPENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

**Table 2: Adverse Reactions Occurring in ≥1% of the DUXPENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6-Month Safety Pool)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUXPENT 200 mg Q2W N=779 n (%)</th>
<th>AS Trials 1 and 2</th>
<th>Placebo N=792 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
<td>50 (6%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

*Injection site reactions cluster includes edema, edema, pruritus, pain, and inflammation.

DUXPENT = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions [see Warnings and Precautions (5.2)]. Injection site reactions were most common with the loading (initial) dose. The safety profile of DUXPENT through Week 52 was generally consistent with the safety profile observed at Week 24.

**Chronic Rhinosinusitis with Nasal Polyps**

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyps (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (CSNP Trials 1 and 2). The safety pool consisted of data from the first 24 weeks of treatment from both studies. In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the DUXPENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUXPENT and at a higher rate than in their respective comparator group in CSNP Trials 1 and 2.

**Table 3: Adverse Reactions Occurring in ≥1% of the DUXPENT Group in CSNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUXPENT 300 mg Q2W N=440 n (%)</th>
<th>CSNP Trial 1 and 2</th>
<th>Placebo N=282 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>28 (6%)</td>
<td>12 (4%)</td>
<td></td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Adenopathy</td>
<td>14 (3%)</td>
<td>5 (2%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>0 (1%)</td>
<td>0 (1%)</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>5 (1%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (1%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

*Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.

Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

The safety profile of DUXPENT through Week 52 was generally consistent with the safety profile observed at Week 24.

**Specific Adverse Reactions**

**Conjunctivitis**

During the 52-week treatment period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUXPENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUXPENT and placebo. In the 52-week CSNP study (CSNP Trial 2), the frequency of conjunctivitis was 5% in the DUXPENT subjects and 1% in the placebo subjects; all of these subjects recovered [see Warnings and Precautions (5.2)].

**Eczema Herpeticum and Herpes Zoster**

The rate of eczema herpeticum was similar in the placebo and DUXPENT groups in the atopic dermatitis trials. Herpes zoster was reported in <1% of the DUXPENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUXPENT + TCS asthma trial, herpes zoster was reported in <1% of the DUXPENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUXPENT and placebo. Among CRSwNP patients, there were no reported cases of herpes zoster or eczema herpeticum.

**Hypersensitivity Reactions**

Hypersensitivity reactions were reported in <1% of DUXPENT-treated subjects. These included conjunctivitis, allergic conjunctivitis, angioedema, anaphylaxis, and urticaria.

**Endothelial and Sympathetic Nervous System Events**

Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUXPENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; ~2% exhibited persistent ADA responses, and ~2% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUXPENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; ~4% exhibited persistent ADA responses, and ~4% had neutralizing antibodies.

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUXPENT; ~2% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUXPENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; ~3% exhibited persistent ADA responses, and ~5% had neutralizing antibodies.

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUXPENT; ~1% exhibited persistent ADA responses, and ~1% had neutralizing antibodies.

The antibody titers detected in both DUXPENT and placebo subjects were mostly low. In subjects who received DUXPENT, development of high titer antibody responses to dupilumab was associated with lower serum dupilumab concentrations [see Clinical Pharmacology (12.3) in the full prescribing information].

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUXPENT therapy [see Warnings and Precautions (5.1)].

**7. DRUG INTERACTIONS**

**7.1 Live Vaccines**

Avoid use of live vaccines in patients treated with DUXPENT.
7.2 Non-Live Vaccines
Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPLEXIN administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPLEXIN during pregnancy. Please contact 1-877-311-8972 or go to https://mothersofbaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Risk Summary
Available data from case reports and case series with DUPLEXIN use in pregnant women have not established a drug-associated risk for subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis after parturition at doses up to 10-times the maximum recommended human dose (MRHD) (see Data). There is limited background information on the safety of DUPLEXIN use in pregnant monkeys for subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis after parturition at doses up to 10-times the maximum recommended human dose (MRHD) (see Data). There is limited background information on the safety of DUPLEXIN use in pregnant monkeys for subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis after parturition at doses up to 10-times the maximum recommended human dose (MRHD) (see Data).

Clinical Considerations
Disease-Associated Maternal and/or Embryo-fetal Risk
In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the newborn. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data
Animal Data
In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on maternal or fetal outcomes were observed in offspring. The estimated background risk of major birth defects and miscarriage for the indicated indications are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation
Risk Summary
There are no data on the presence of dupilumab in human milk, the effects of dupilumab in breastfed infants, or the effects on milk production. Milk production was not assessed in human milk feedings. The effects of dupilumab on the breastfed infant are unknown. The effects of dupilumab on milk production are unknown. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DUPLEXIN and any potential adverse effects on the breastfed child from DUPLEXIN or from the underlying maternal condition.

8.3 Pediatric Use
Asthma
A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPLEXIN (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with placebo. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight (see Clinical Pharmacology (12.3) in the full prescribing information). The adverse event profile in adolescents was generally similar to the adults (see Adverse Reactions (6.1)).

CRSwNP does not normally occur in children. Safety and efficacy in pediatric patients (<18 years of age) with CRSwNP have not been established.

References:
An Overview of Digital Therapeutics (DTx) and Relevant Regulation

**Digital Therapeutics (DTx)** provide patients with evidence-based therapeutic solutions that are driven by high-quality software programs. These solutions can prevent, manage, or treat a medical disorder or disease and are used both independently or alongside medications, devices, and other therapies. These products leverage advanced technology to bolster design, clinical evaluation, usability, and data security. What follows in this piece are some highlights of a presentation of DTx principles given at AMCP Nexus 2019.

**What Are DTx Solutions?**
These therapeutic solutions are reviewed and cleared or approved by regulatory agencies to support product claims regarding efficacy, risk, and therapeutic intention. DTx products, according to the presenters, are a distinct subset of solutions within the broader digital health landscape, which consists of mobile health, health information technology, devices, sensors, wearables, personalized healthcare, and telehealth solutions.

To be formally considered a DTx, a product must adhere to several foundational principles, including prevention, management, or treatment of a medical disorder or disease, incorporation of software, emphasis on patient privacy and security, and presence of clinically relevant evidence supported by reliable research. Digital health products that don’t claim to manage or treat a disease are not subjected to the same standards as DTx. Many products in this category include lifestyle and fitness apps, medication adherence tools, telehealth and telemedicine platforms, and other similar technologies.

The International Medical Device Regulators Forum (IMDRF) allows national regulatory bodies to discuss future directions in medical device regulation. This voluntary group of international medical device regulators works to accelerate globalized medical device regulatory synchronization and collaboration. Members include Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the United States, with the World Health Organization (WHO) as an observer.

**Software as Medical Devices**
Software as a Medical Device (SaMD) is defined as software intended to be used for one or more medical purposes without being part of the device’s hardware. This definition was created by IMDRF and it is being integrated into regulatory frameworks internationally. DTx go through the European qualification and review process in Europe and the Food and Drug Administration (FDA) in the United States.

The presenters referenced several DTx technologies, including reSET, a software app that is prescribed by physicians to treat patients with substance use disorder. Other solutions referenced include Propeller, designed to treat asthmatic patients who are uncontrolled on current therapy and patients with chronic obstructive pulmonary disease (class II-JV). Bluestar and Insuylia, two FDA-approved apps for type 2 diabetes management, and Kaia Health, an FDA-approved app therapy for chronic back pain patients, were among the others mentioned.

**Presentation:** Coder M, Patterson B, et al. Expanding the Managed Care Professional’s Digital Therapeutics IQ. Presented at: AMCP Nexus 2019; October 29 – Nov 1; National Harbor, MD.

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**A Health Care Reform Update: The ACA, Trump Administration’s Impact, and Public Perception**

**Costs Remain A** central concern for many Americans, according to an in-depth presentation regarding the current state of health care reform and updates regarding the current political situation and its effects on health care reform presented by Melissa Andel, MPP, Vice President of Health Policy Applied Policy, at AMCP Nexus 2019.

**Overview of Current State of Affairs**
Beginning with the current state of health insurance coverage in the U.S., Andel noted that employer-sponsored coverage continues to be the main source of coverage for Americans and that roughly 3% of Americans are covered through marketplace plans. It is estimated that 209 million Americans have gained coverage through the Affordable Care Act (ACA). Andel added that after dropping in 2014-2016, the rate of uninsured Americans began to increase in 2017 and has continued to do so, despite still being below pre-ACA levels. According to the presentation, Americans aged 18-34, women, and those living in households making less than $48,000 annually have seen the greatest increases in uninsurance rates since 2016, as per a January 2019 Gallup poll.

Andel also stated that premiums are above claims costs on average, but that experiences can be highly variable between states and between plans. The growth in claim costs

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19
seen early in 2019 indicated the repeal of individual mandate and the expansion of short-term insurance plans didn’t leave the individual market significantly less healthy. The participation of insurers in 2020 is expected to increase in comparison to current participation in 2019.

Andel listed some key takeaways for the current state of U.S. health insurance coverage:

- Know your market and don’t get distracted by headlines: the primary source of insurance coverage for Americans continues to be employer-sponsored, followed by Medicare and Medicaid.
- While there has been a recent increase in the uninsured rate, we are not near pre-ACA levels of uninsurance (at least nationally).
- Enrollment in the Exchange market appears to be stabilizing (though it is an inherently unstable market).
- Financial performance of plans indicates that individual Exchange market premiums are priced “right” and may be stabilizing.
- There are large variations in experience from state to state.

**Current Administration Actions and Their Effects**

Regarding the Trump Administration’s actions, Andel begins by addressing the underlying issue with cost-sharing reduction payments. She noted that exchange plans must provide cost-sharing reductions (CSRs) to enrollees with incomes between 100%-250% of FPL and that legislation did not appropriate funds for the government to refund plans for value of CSRs, adding that the Obama Administration had been using funds from another source to make payments to plans that the Trump Administration stopped payments for in October 2017. Issuers in most states responded to this cessation in CSR payments by including costs of CSRs in premium calculation for Silver plans only. This “Silver Loading” is expected to result in higher federal costs, with additional subsidies and an increase in premium tax credit value expected to increase federal costs by approximately $10 billion between 2019 – 2021.

**Here in 2019...**

Speaking on 2019 being the first year without the mandate, Andel states that Americans will no longer face a tax penalty for failing to carry ACA-compliant health insurance, and brought up two concerns regarding this development: Americans not carrying insurance, and the resulting risk-pool of Americans carrying insurance, particularly through the exchanges.

Her key takeaways for the current administration’s impact on health insurance coverage were as follows:

- Public concern over health care as an issue has shifted from coverage to cost.
- Drugs (and health plans) have become the target of anger over health care prices and therefore the driver of policy proposals.
- Americans may like the idea of Medicare for All, but also seem to think they will keep their ESI under the plan.
- The path that consistently garners public support is a Medicare/Medicaid buy-in option.

**Popularity of the ACA**

The ACA has become more popular over time, as per figures presented by Andel. The opinion on employer-sponsored insurance is more complicated, however, with affordability at the apex of citizens’ concerns. Americans, Andel’s presentation noted, are blaming pharmaceutical and health plans for current high costs, and although most are receptive to Medicare for all/single-payer, they don’t appear to believe there will be much of a change.

Andel’s key takeaways regarding how Americans view the ACA, and health care in general, were as follows:

- Public concern over health care as an issue has shifted from coverage to cost.
- Drugs (and health plans) have become the target of anger over health care prices and therefore the driver of policy proposals.
- Americans may like the idea of Medicare for All, but also seem to think they will keep their ESI under the plan.
- The path that consistently garners public support is a Medicare/Medicaid buy-in option.

**Approaches to Value-Based Contracting with Clinical Strategies**

**EStabLished in 2017,** the UPMC Center for Value-Based Pharmacy Initiatives (VBPI), housed within the UPMC Center for High-Value Health Care, a non-profit research entity within the UPMC Insurance Services Division, has developed in collaboration with UPMC Health Plan Pharmacy, striving to promote greater value in medication use both within and outside of UPMC.

A new presentation by UPMC’s Chester Good, MD, MPH, and Jessica Daw, PharmD, MBA, given at AMCP Nexus...
2019, explored the various models for value-based contracts, modified Delphi surveys, epidemiological analyses, and clinical initiatives. Using multiple sclerosis (MS) to portray value-based care (VBC), the presenters explained that prior MS VBCs were based on surrogate clinical indicators like MS-related ED visits, hospitalizations, adherence, relapse rates. They noted that the VBPI Delphi Survey, however, unanimously ranked “worsening physical disability” as the most meaningful MS outcome. This led to the creation of a novel approach to VBC based on patient-reported disability progression. This VBC is supported by the MS Clinical Wrap Around Program.

The contracting process with VBCs is longer than typical contracting and is much more granular. Risks are still very low and driven by the concerns of pharmaceutical brand teams. They are therefore often considered tilted towards the pharma side. The presenters identified two-sided risk as a method to advance conversation. Regarding data availability, they noted that Delphi results are not available in the dataset, that proxy data on limited population is generalizable across the entire population, and that there is a wide variation around data availability across plans.

The UPMC presenters went on to list diabetes, cardiac, opioid/MAT, and MS as therapeutic areas of focus for clinical programs. They noted that over 57% of the 1,200 referred diabetes cases involved intervention communicating to the provider office directly to remedy therapeutic complications.

The following statistics are presented regarding the diabetes clinical program:

- Eight potentially avoided ED visit or Inpatient hospital stay.
- 180 avoided unnecessary office visit or unnecessary medication.
- 598 coordinated care, lowered medication costs, or provided education to member.

The change in the total cost of care for members participating in the MS clinical program was evaluated by comparing data taken six months before program initiation to that taken six months after. The MS program was found to be associated with a significant decrease in medical costs and a significant increase in pharmacy costs driven by increased utilization.

**PRESENTATION: Good C, Daw J, et al. Innovative Value-Based Contracting Approaches with Comprehensive Clinical Strategies.**

**SCIENCE AND INNOVATION THEATER**

**A Biosimilar Oncology Therapy for Patients: Totality of Evidence**

**EARLIER THIS YEAR**, the Food and Drug Administration (FDA) approved bevacizumab-awwb, the first oncology therapeutic biosimilar to receive FDA approval. Marketed under the name MVASI and manufactured by Amgen, bevacizumab-awwb was proven similar to its reference drug, bevacizumab (marketed as Avastin).

Similar safety and efficacy outcomes between bevacizumab-awwb and bevacizumab were demonstrated through the MAPLE trial, the results of which were presented in a Science and Innovation Theater at AMCP Nexus 2019. The presentation looked specifically at a comparative clinical study of patients with advanced nonsquamous non–small cell lung cancer (NSCLC).

The final analysis included 328 bevacizumab-awwb patients and 314 bevacizumab patients. Response rates were similar between the bevacizumab-awwb (39.0%, n = 128) and bevacizumab groups (41.7%, n = 131). Progression-free survival rates at the conclusion of the study were 60.1% (n = 197) and 60.2% (n = 189) in the bevacizumab-awwb and bevacizumab groups, respectively. By the end of the study, there were 43 deaths (13.3%) in the bevacizumab-awwb group and 36 deaths (11.7%) in the bevacizumab group.

Overall occurrence of adverse events (AEs) did not significantly differ between the groups: the rate of any AE in the bevacizumab-awwb group was 95.1% (n = 308), compared to 93.5% (n = 289) in the bevacizumab group. Rates of serious and fatal AEs were 26.2% (n = 85) and 4.0% (n = 13) in the bevacizumab-awwb group, respectively, versus 23.0% (n = 71) and 3.6% (n = 11) in the bevacizumab group, respectively.

Grade ≥ 3 adverse events of interest (EOIs) were similar between the groups. The rate of any EOI was 31.5% (n = 102) in the bevacizumab-awwb group compared to 32.0% (n = 99) in the bevacizumab-awwb group; hypertension, 6.8% (n = 22) versus 5.5% (n = 17), respectively; gastrointestinal perforation, 0.9% (n = 3) versus 1.3% (n = 4), respectively; pulmonary hemorrhage, 0.6% (n = 2) versus 1.6% (n = 5), respectively; wound healing complications, 0.3% (n = 1) versus 0.6% (n = 2); and proteinuria, 0.3% (n = 1) for each.

**PRESENTATION: Loaiza-Bonilla A. A Biosimilar Oncology Therapy for Patients: Totality of Evidence.**

**SCIENCE AND INNOVATION THEATER: Loaiza-Bonilla A. A Biosimilar Oncology Therapy for Patients: Totality of Evidence.**

Presented at: AMCP Nexus 2019; October 29 – Nov 1; National Harbor, MD.
See life break through

Advancing oncology at the speed of life™