Help your mild-to-moderate plaque psoriasis patients show their unexpected with the proven power of SERNIVO® Spray.

**PROGRESS YOU CAN SEE**

Improvement in psoriatic plaque on the knee over 28 days of treatment.

**POWERFUL RESULTS**

Investigator’s Global Assessment of treatment success.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 14</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Actual Patient. Individual results may vary.

Visit SERNIVO.com for terms and conditions and full eligibility requirements.

*In psoriasis treatment, hairy body areas with creases are often considered to be difficult to treat.* Standard photographs of lesions on the knee, hairy extensor forearm, and shin were taken at Days 1, 8, 14, and 29. Visible results may vary.

Pooled data based on results from 2 randomized, controlled studies of adults with moderate plaque psoriasis with similar methodology. Subjects were randomized to either SERNIVO (n=356), dipropionate spray 0.05%, or vehicle (n=182). Treatment success was defined as an Investigator’s Global Assessment (IGA) of 0 or 1 (clear or almost clear) and at least a 2-grade reduction in redness and scaling by day 29.

**IMPORTANT SAFETY INFORMATION**

SERNIVO Spray can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. Systemic effects of topical corticosteroids may also manifest as Cushing’s syndrome, hyperglycemia or unmasking of latent diabetes mellitus, and glucosuria. These effects of topical corticosteroids may also manifest as Cushing’s syndrome, linear growth retardation, delayed bone maturation, and intracranial hypertension have been reported with the use of corticosteroids in pediatric patients. Rare systemic effects such as Cushing’s syndrome, perioral dermatitis, allergic contact dermatitis, and skin atrophy are rare and generally occur after prolonged exposure to larger than recommended doses, particularly with high-potency topical corticosteroids. Do not use if atrophy is present at the treatment site. Do not use with occlusive dressings. Avoid use on the face, scalp, axilla, groin or other intertriginous areas.

Use of SERNIVO Spray is not recommended in pediatric patients as they are more susceptible to systemic toxicity. Allergic contact dermatitis may occur.

The most common adverse reactions (≥1%) were application site pruritus, burning and/or stinging, pain, and atrophy. Local reactions and skin atrophy are more likely to occur with occlusive use, prolonged use, or use of higher potency corticosteroids. These are not all the possible side effects of SERNIVO Spray.

Visit Full Prescribing Information at SERNIVO.com and brief summary of prescribing information on adjacent page.

**INDICATION AND USAGE**

SERNIVO Spray is indicated for the treatment of mild-to-moderate plaque psoriasis in patients 18 years of age or older.

To report SUSPECTED SIDE EFFECTS, call Promius Pharma at 1-888-966-8766 or contact the FDA at 1-800-FDA-1088.

**REFERENCES**


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Rx Only

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

SERNIVO Spray is indicated for the treatment of mild to moderate plaque psoriasis in patients 18 years of age or older.

**DOSEAGE AND ADMINISTRATION**

Apply SERNIVO Spray to the affected skin areas twice daily and rub in gently.

Use SERNIVO Spray for up to 4 weeks of treatment. Treatment beyond 4 weeks is not recommended.

Avoid use on the face, scalp, axilla, groin, or other intertriginous areas.

SERNIVO Spray is for topical use only. It is not for oral, ophthalmic, or intravaginal use.

**CONTRAINdications**

None.

**WARNINGS AND PRECAUTIONS**

**Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression and Other Unwanted Systemic Glucocorticoid Effects**

SERNIVO Spray can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency. This may occur during or after withdrawal of treatment. Factors that predispose to HPA axis suppression include the use of high-potency corticosteroids, large treatment surface areas, prolonged use, use of occlusive dressings, altered skin barrier, liver failure, and young age.

Evaluation for HPA axis suppression may be done by using the adrenocorticotropic hormone (ACTH) stimulation test.

In a study including 48 evaluable subjects 18 years of age or older with moderate to severe plaque psoriasis, abnormal ACTH stimulation test results suggestive of adrenal suppression were identified in 5 out of 24 (20.8%) subjects after treatment with SERNIVO Spray twice daily for 15 days. No subject (0 out of 24) had abnormal ACTH stimulation test results after treatment with SERNIVO Spray twice daily for 29 days (see Clinical Pharmacology).

If HPA axis suppression is documented, gradually withdraw the drug, reduce the frequency of application, or substitute with a less potent corticosteroid. If signs and symptoms of steroid withdrawal occur, supplemental systemic corticosteroids may be required.

Systemic effects of topical corticosteroids may also manifest as Cushing’s syndrome, hyperglycemia, and glucosuria. These events are rare and generally occur after prolonged exposure to larger than recommended doses, particularly with high-potency topical corticosteroids.

Minimize the unwanted risks from endocrine effects by mitigating the risk factors favoring increased systemic bioavailability and by using the product as recommended [see Dosage and Administration].

Pediatric patients may be more susceptible to systemic toxicity due to their larger skin surface to body mass ratios. Use of SERNIVO Spray is not recommended in pediatric patients [see Use in Specific Populations].

**Allergic Contact Dermatitis**

Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Corroborate such an observation with appropriate diagnostic patch testing. If irritation develops, discontinue the topical corticosteroid and institute appropriate therapy.

**ADVERSE REACTIONS**

**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 clinical practice. In two randomized, multicenter, prospective vehicle-controlled clinical trials, subjects with moderate plaque psoriasis of the body applied SERNIVO Spray or vehicle spray twice daily for 4 weeks. A total of 352 subjects applied SERNIVO Spray and 180 subjects applied vehicle spray.

Adverse reactions that occurred in at least 1% of subjects treated with SERNIVO Spray for up to 28 days are presented in Table 1.

**Table 1: Adverse Reactions Occurring in ≥1% of Subjects Treated with SERNIVO Spray for up to Four Weeks**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>SERNIVO Spray b.i.d. (N=352)</th>
<th>Vehicle Spray b.i.d. (N=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application site pruritus</td>
<td>6.0%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Application site burning and/or stinging</td>
<td>4.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Application site pain</td>
<td>2.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Application site atrophy</td>
<td>1.1%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Less common adverse reactions (with occurrence lower than 1% but higher than 0.1%) in subjects treated with SERNIVO spray were application site reactions including telangiectasia, dermatitis, discoloration, folliculitis and skin rash, in addition to dysgeusia and hyperglycemia. These adverse reactions were not observed in subjects treated with vehicle.

**Postmarketing Experience**

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

**Pregnancy Category C**

There are no adequate and well-controlled studies in pregnant women. SERNIVO Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Betamethasone dipropionate has been shown to be teratogenic in rabbits when given by the intramuscular route at doses of 0.05 mg/kg. The abnormalities observed included umbilical hernias, cephaloceles, and cleft palate.

**Nursing Mothers**

Systemically administered corticosteroids appear in human milk and can suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids can result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when SERNIVO Spray is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness of SERNIVO Spray in patients younger than 18 years of age have not been studied; therefore use in pediatric patients is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at greater risk of systemic toxicity, including HPA axis suppression and adrenal insufficiency, when treated with topical drugs. [see Warnings and Precautions]

Rare systemic effects such as Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients, especially those with prolonged exposure to large doses of high potency topical corticosteroids.

Local adverse reactions including skin atrophy have also been reported with use of topical corticosteroids in pediatric patients.

**Geriatric Use**

Clinical studies of SERNIVO Spray did not include sufficient numbers of subjects who were 65 years of age or older to determine whether they respond differently from younger subjects.

Manufactured by: DPT Laboratories, Ltd., San Antonio, TX 78215
Distributed by: Promius Pharma, LLC., Princeton, NJ 08540
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Issued: 02/2016
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Expected Changes to Health Plan Coverage Policies

In 2013, roughly 293 million lives were covered by various payer groups, 39% of which were via government enrollment through Medicaid and Medicare and other government agencies. In 2018, there are an estimated 298 million lives covered, 47% of which are through government enrollment. By 2023, there will be a projected 310 million lives covered, 51% of which will be through government enrollment.

During a presentation at Nexus 2018, Dan Mendelson, MPP, founder of Avalere Health, discussed the coverage and formulary changes in insurance and identified certain pharmaceutical policy changes.

Between 2008 and 2018, payers have increasingly used high tiers and management. In 2008, just 7% of plans reported having four or more drug benefit tiers, while in 2018, that number has jumped to 51%.

Recent policy changes have also offered more flexibility for Medicare Advantage (MA) plan growth, which will allow these plans to offer a wider array of supplemental benefits beginning next year. States have been seeking new Medicaid flexibilities through waivers; the most recent developments include Oklahoma negotiating supplemental rebates based on drug outcomes and Louisiana pursuing innovative payment models for high-cost treatments for hepatitis C.

Mr. Mendelson said areas of future focus for payers include:

- Increasing the use of data to drive care management and decision-making
- Providing targeted services to certain enrollees to boost return
- Influencing provider behavior, particularly in referrals and prescribing
- Implementing innovative contracting arrangements with providers
- Delivering healthcare, not just health insurance
- Focusing on consumer engagement through digital and benefit design

According to an Avalere Health survey of 50 decision-makers representing 49 health plans and 183 million covered lives, 98% said they are familiar with outcomes-based contracts (OBCs) for drugs, 61% have one or more OBCs in place (25%) or are in negotiations for one (34%), and 52% perceive OBCs as having cost-saving potential.

Next, Mr. Mendelson discussed the recently released “American Patients First” blueprint from the U.S. Department of Health & Human Services and the Trump administration. Key themes include:

- Enhanced competition, management, and negotiation
  - Generic and biosimilar development and adoption
  - Medicare Part B benefit management
  - Third-party vendor negotiations in Medicare Part B
  - Pharmacy benefit manager and rebate system incentives
  - Formulary flexibility for Medicare Part D plans
- Transparency
  - List prices in direct-to-consumer advertising
  - Transparency into Medicare and Medicaid prices and international price disparities
  - Medicare Part D pharmacist disclosure
- Value-driven incentives
  - Value-based payment models
  - Indication-based pricing
  - Long-term financing approaches

He concluded by providing the following forward-thinking strategies:

- MA growth, plan innovation to tailor benefit packages under new flexibilities, and ancillary support
- Vertically integrated acquisitions, driven by the new economics of value
- Change in pharmaceutical pricing and purchasing approaches resulting from policy pressure and the shift to value-based payments
- Data, analytic, intervention, and reporting capabilities to drive competitive advantage in plans, providers, and pharmaceutical sectors

Presentation HR: Ready or Not: The Impact of Health System and Policy Change on Managed Care Pharmacy. AMCP Nexus 2018.
Bleed Size 8.25 x 11

Powerful migraine relief made simple

ZEMBRACE SymTouch may be an appropriate option for your patients who experience:

- migraine with nausea
- rapid onset migraine
- morning migraine

**Indication and Usage**

ZEMBRACE SymTouch is indicated for the acute treatment of migraine with or without aura in adults.

**Limitations of Use:**
- Use only if a clear diagnosis of migraine has been established. If a patient has no response to the first migraine attack treated with ZEMBRACE SymTouch, reconsider the diagnosis before ZEMBRACE SymTouch is administered to treat any subsequent attacks.
- ZEMBRACE SymTouch is not indicated for the prevention of migraine attacks.

**Important Safety Information**

ZEMBRACE SymTouch is contraindicated in patients with:
- Ischemic Coronary Artery Disease (CAD) or coronary artery vasospasm (including Prinzmetal’s angina), Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders
- Uncontrolled hypertension, history of stroke or transient ischemic attack (TIA) or history of hemiplegic or basilar migraine
- Peripheral vascular disease
- Ischemic bowel disease
- Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot derivatives, or another 5-HT1 agonist
- Concurrent or recent (within 2 weeks) use of an MAO-A inhibitor
- Known hypersensitivity to sumatriptan
- Severe hepatic impairment

There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan injection. Some of these reactions occurred in patients without known CAD, 5-HT1 agonists, including ZEMBRACE SymTouch, may cause coronary artery vasospasm. Life-threatening disturbances of cardiac rhythm leading to death in some cases, have been reported within a few hours following the administration of 5-HT1 agonists. Cerebrovascular events including cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT1 agonists; and some have resulted in fatalities. Discontinue ZEMBRACE SymTouch if any of these events occur. Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors prior to receiving ZEMBRACE SymTouch. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of ZEMBRACE SymTouch in a medically supervised setting and consider periodic follow up. Sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan injection and are usually non-cardiac in origin. ZEMBRACE SymTouch may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction, splenic infarction, and Raynaud’s syndrome. Overuse of acute migraine drugs may lead to exacerbation of headache (medication overuse headache). Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms may be necessary. Serotonin syndrome may occur with ZEMBRACE SymTouch, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors. Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT1 agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with ZEMBRACE SymTouch. Discontinue ZEMBRACE SymTouch if serotonin syndrome is suspected or hypertensive crisis is observed. Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. ZEMBRACE SymTouch should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold. Most common adverse reactions (≥5% and > placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness. These are not all the side effects associated with ZEMBRACE SymTouch. Advise the patient to read the FDA-approved patient labeling. Please see Patient Information, Instructions For Use and Full Prescribing Information for ZEMBRACE SymTouch. You are encouraged to report negative side effects of prescription drugs. To report SUSPECTED SIDE EFFECTS, call Promius Pharma at 1-888-966-8766 or contact the FDA at 1-800-FDA-1088 (1-800-332-1088) or online at http://www.fda.gov/Safety/MedWatch. Please see Brief Summary of Prescribing Information on the adjacent page. References:


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Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, combination of these drugs for 10 or more days per month) may lead to exacerbation of headache (overuse headache). Medication overuse headache may present as migraine-like daily headache or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Serotonin Syndrome

Serotonin syndrome may occur with ZEMBRACE SymTouch injection, particularly during co-administration with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tryptophan, and monoamine oxidase inhibitors (MAOIs). Serotonin syndrome may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue ZEMBRACE SymTouch injection if serotonin syndrome is suspected.

Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients with a history of hypertension. Monitor blood pressure in patients treated with ZEMBRACE SymTouch. ZEMBRACE SymTouch injection is contraindicated in patients with uncontrolled hypertension.

Anaphylactic Reactions

Anaphylactic reactions have occurred during administration of sumatriptan. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to a drug allergen. ZEMBRACE SymTouch injection is contraindicated in patients with a history of hypersensitivity reaction to sumatriptan.

Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. ZEMBRACE SymTouch injection should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of another drug and may not reflect the rates observed in practice. ZEMBRACE SymTouch injection is contraindicated in patients with a history of severe orthostatic hypotension.

Table 1: Adverse reactions that occurred in ≥ 2% placebo-controlled clinical trials in migraine subjects (Studies 2 and 3), following either a single 6 mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of ≥2% in more than one group treated with sumatriptan injection 6 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1- Adverse Reactions in Pooled Pla cebo-Controlled Trials in Patients with Migraine (Studies 2 and 3)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Sumatriptan Injection 6 mg Subcutaneous (n = 547)</th>
<th>Placebo (n = 370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of Subjects Reporting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical sensations</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>Tingling</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Warmth sensation</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Feeling of heaviness</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pressure sensation</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Feeling of tightness</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Numbness</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Feeling strange</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tight feeling in head</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Tightness in chest</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pressure in chest</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat discomfort</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Discomfort: nasal cavity/sinus</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>59</td>
<td>24</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaw discomfort</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakness</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neck pain/stiffness</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>0</td>
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</tbody>
</table>
Access and Reimbursement Considerations for CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapies use a patient’s T cells to fight various cancers. These agents can provide longer-term survival benefits, but are associated with dangerous adverse events, including cytokine release syndrome and neurologic toxicity. In addition to clinical toxicity, these agents carry a list price of nearly half a million dollars for a single infusion, “shattering oncology drug pricing norms.” As of June 2018, 1,000 U.S. patients have received FDA-approved commercial CAR T-cell therapy.

During a presentation at Nexus 2018, Therese Mulvey, MD, director of quality safety and value at Massachusetts General Cancer Center and Affiliate Network, and Stephanie Tran, PharmD, clinical consultant pharmacist at UMass Medical School – Clinical Pharmacy Services, discussed access, affordability, and reimbursement for these agents. Payers need to consider coverage, network, payment rate, and payment timing. In the Centers for Medicare & Medicaid Services’ (CMS) inpatient prospective payment system proposed rule, they presented several reimbursement options for CAR T-cell therapies in fiscal year 2019:

- Assignment of a new technology add-on payment to CAR-T products
- Assignment of CAR-T claims to Medicare Severity Diagnosis Related Group (MS-DRG) 016
- Implementation of a cost-to-charge ratio of 1.0 for CAR-T products
- Creation of a new MS-DRG that incorporates a portion of the product cost
- Alternative approaches and authorities to encourage value-based care and lower drug prices

A final evidence report from the Institute for Clinical and Economic Research earlier this year found that the two FDA-approved CAR T-cell agents (tisagenlecleucel and axicabtagene ciloleucel) provide net health benefits versus standard chemoimmunotherapy and are cost-effective in the long term. At current costs, only 38% of the eligible population of 5,900 could be treated with axicabtagene ciloleucel before crossing the affordability threshold.

Potential affordability solutions for these high costs include value-based contracting, indication-based pricing, and value-based pricing, as well as discounts, reinsurance, amortization, and a subscription model.

A report from Healio found that the estimated majority of payments for tisagenlecleucel for the treatment of acute lymphocytic leukemia are from commercial/employer insurance (55%), while the majority of payments for axicabtagene ciloleucel for diffuse large B-cell lymphoma are from Medicare (50%).

The speakers gave an example of Massachusetts Medicaid program (MassHealth) that carved out coverage of CAR T-cell therapies to be managed under the pharmacy benefit rather than adjudicated payment per discharge (APAD). In February, MassHealth notified providers of the intended carve out and sent out contract amendments. The carve out was effective March 1, with additional edits made during the review period. CMS approved the state plan amendment on June 22.

With the carve out, separate bills that included a copy of the invoice for CAR T-cell product were submitted as a professional claim on 837p form. This was not included in the APAD rate, thus MassHealth could claim the rebate for these agents. They said the benefits of a carve out method include managing these agents as a pharmacy benefit regardless of site of administration, ensuring that hospitals are properly reimbursed with consideration of the price of outlier treatments, and protecting payers when outcomes-based agreements exist.

An Eye on the Pipeline: High-Impact Drugs in 2019 and 2020

High-impact drugs can be identified through their clinical and economic impact. Proactive pharmaceutical pipeline monitoring and budget impact analyses can help payers anticipate the budget impact.

During a presentation at Nexus 2018, Nicole Trask, PharmD, clinical consultant pharmacist at the University of Massachusetts Clinical Pharmacy Services, gave an update on high-impact specialty drugs in the 2019 and 2020 pharmaceutical pipeline.

AVXS-101 FOR SPINAL MUSCULAR ATROPHY (SMA)
The single-arm, open-label, multicenter, phase 3 STR1VE trial included 11 children <6 months with type 1 SMA who received a single intravenous dose of AVXS-101. The event-free survival one or more months post-treatment was 100%. This agent could provide a one-time treatment for the underlying cause of SMA, but long-term efficacy data are needed. Cost data are not yet available, but the estimated budget impact is approximately $1.5 million per patient, or $9 million per year.

RVT-802 FOR COMPLETE DIGEORGE ANOMALY
A clinical trial including 60 patients with complete DiGeorge anomaly who received RVT-802 resulted in a survival rate of greater than 70%. Among the 43 patients alive at the time of analysis, the median survival was 4.7 years (range, 6 months to 16 years). This treatment could provide a significant survival benefit for a uniformly fatal disease; however, it does not correct the underlying defects in chromosome 22 that cause the disease. Cost data are not yet available, but the estimated budget impact is approximately $1.5 million per patient.

FITUSIRAN FOR HEMOPHILIA
The open-label, phase 2 extension OLE study assessed the use of fitusiran 50 mg or 80 mg administered subcutaneously once monthly in 33 adult men with moderate or severe clinically stable hemophilia A or B. Most patients (70%) reported adverse events (AEs), including two patients who reported serious AEs. During the observation period, 48% of patients were bleed-free, and 67% of patients had no spontaneous bleeds. The annualized bleeding rate (ABR) in the 14 patients with inhibitors was 38 events per year presstudy compared with zero events after treatment. This agent could significantly reduce ABR in this difficult-to-treat population. Cost data are not yet available, but the estimated budget impact is approximately $400,000 per patient.

REMESTEMCEL-L FOR ACUTE GRAFT-VERSUS-HOST DISEASE (aGVHD)
An open-label, multicenter, phase 3 study assessed 55 children 2 months to 17 years with steroid-refractory aGVHD who received remestemcel-L $2\times10^6$ intravenously twice weekly for four weeks. The overall response rate (ORR) at 28 days was 69% in the treated group compared with 45% in a historical control group (P=0.0003). At day 100, there was an 87% survival rate among the 38 patients who achieved ORR at day 28. This agent, however, may have lower efficacy in adults. Cost data are not yet available, but the estimated budget impact is approximately $375,000 per patient.

LAROTRECTINIB FOR NTRK GENE FUSION
An open-label, dose-escalation, phase 2 study assessed 55 adults and adolescents with TRK fusion-positive tumors who received larotrectinib 100 mg orally twice daily until disease progression. The ORR was 75% according to an independent review and 80% according to the investigator assessment. At one year, 71% of responses were ongoing, and 55% of patients had no disease progression. This agent could effectively target cancer based on the presence of a biomarker. Cost data are not yet available, but the estimated budget impact is approximately $180,000 per patient.

“The approval of high-cost gene therapies may highlight the need for innovative payment models.”

—Nicole Trask, PharmD

ICER’s Role in Payer Decision-Making

Researchers analyzed the current and potential impact of Institute for Clinical and Economic Review (ICER) assessments on payer decisions. They found that, according to payers, ICER has the potential to provide unbiased clinical and economic evaluations. However, the organization’s late timing of reports and a less-than-transparent evaluation process are limitations. The results of the study were presented at Nexus 2018 during a poster session titled “Formulary Decision-Maker Perspectives on ICER Impact.”

The researchers invited 422 U.S. formulary decision-makers to participate in a 23-question web-based survey in July 2018. Respondents were required to be involved in making drug coverage decisions in their current role or within the past two years. Among those invited, 22 respondents met the inclusion criteria; they represent 121.2 million covered lives. Almost all respondents (95%) believe that a Health Technology Assessment-like body is needed, but 87% believe that ICER is only slightly to somewhat influential on their organization.

Ninety-five percent said ICER’s use of quality-adjusted life-years are little to somewhat useful. Sixty-eight percent reported most commonly using ICER reports during pharmacy and therapeutics review, while 60% said they most often use the reference section for a literature review as part of the drug information/review process.

Half (50%) reported using the reviews as a negotiation point for rebate/pricing discussions and to inform choice of a preferred product. Payers said they are more likely (37%) than not (5%) to request that a product list price meet an ICER evaluation; 35% said they would be likely to request a rebate >50% of the difference between the list price and cost-effectiveness threshold. Almost half of respondents said their organization has directly referenced an ICER assessment during manufacturer discussions.

The study was sponsored by ICON.


Regulatory and Legislative Efforts to Address the Opioid Crisis

Forty-six people die each day from prescription opioid-related deaths. The states with the highest overdose deaths are West Virginia, Maryland, Maine, and Utah. Among the 20.5 million Americans 12 years and older who had a substance use disorder in 2015, two million involved prescription opioids. Opioid addiction is driving the accidental death rate in the United States.

During a presentation at Nexus 2018, Karen M. Powell, PharmD, MS, pharmacy solutions coordinator at Conduent, Dixit H. Shah, RPh, deputy director of the Maryland Medicaid Pharmacy Program, and Janelle V. Sheen, PharmD, director of clinical services at Conduent, discussed federal and legislative updates on the management of opioids and data-driven strategies for opioid risk management.

According to the White House Council on Economic Advisers, the overall economic cost related to loss of life in 2015 due to the opioid crisis is $500 billion. According to TheFix.com, the largest economic impact came from individuals who lost potential earnings due to addiction or early death. Brookings.edu reports that the U.S. Department of Health & Human Services (HHS) found that nearly three-quarters of states saw an unprecedented number of children entering foster care.

Some states have begun to enact opioid-related prescribing and monitoring legislation, such as prescribing guidelines on dosage, days supply, and morphine milligram equivalents (MME); use of naloxone for overdose prevention; prescription drug monitoring programs; prescriber and patient education; opioid disposal plans; and electronic opioid prescriptions.

The speakers detailed HHS’ five-point strategy to combat the opioid crisis:

1. Access: Better prevention, treatment, and recovery services
2. Data: Better data on the epidemic
3. Pain: Better pain management
4. Overdoses: Better targeting of overdose reversing drugs (like naloxone)
5. Research: Better research on pain and addiction

The Centers for Disease Control and Prevention (CDC) released guidelines for adult patients in the primary care setting that focus on determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Some specific recommendations include starting with immediate-release products, prescribing the lowest effective dose (≤3 days for acute pain and rarely prescribing >7 days for pain), evaluating patients’ history of substance use disorder or concurrent medications (such as benzodiazepines), and incorporating strategies to mitigate risk.

The Centers for Medicare & Medicaid Services also released guidance earlier this year that seeks to improve drug utilization review controls and to address Medicare Part D populations that receive opioids. For its part, the FDA has supported the CDC guidelines and required labeling changes for certain products.

Data can be an important component of opioid risk management.
Halobetasol/tazarotene is a fixed-dose combination lotion of a lower-strength steroid and retinoid that can be used to treat psoriasis. Researchers conducted an actuarial budget impact model to assess cost impacts for this drug. The results of the study were presented at Nexus 2018 during a poster session titled “Cost per Responder Analysis of Guselkumab Versus Ixekizumab Using Efficacy Results from Long-Term Extension Pivotal Clinical Trials in Patients with Moderate to Severe Plaque Psoriasis.”

Researchers assessed the percentage of patients achieving at least 75%, 90% or 100% improvement in Psoriasis Area and Severity Index (PASI) score from baseline during the first year of treatment. Dosing was based on recommendations from the FDA label: eight doses of guselkumab 100 mg and 18 doses of ixekizumab 80 mg. The study assumed that patients took every dose as prescribed in a calendar year, and costs for these agents were based on U.S. wholesale acquisition costs as of April 2018.

At 60 weeks, the PASI 75, 90, and 100 response rates were 96.8%, 83.8%, and 50.0%, respectively, for guselkumab, and 83.0%, 73.0%, and 55.0%, respectively, for ixekizumab.

Drug costs during the first year were $81,268 for guselkumab and $92,909 for ixekizumab. First-year cost per responder for those receiving guselkumab was $91,518 for patients achieving PASI 75, $106,094 for patients achieving PASI 90, and $168,257 for patients achieving PASI 100. For ixekizumab, these costs were $111,938, $127,272, and $168,925, respectively.

The researchers concluded that guselkumab is more cost-effective than ixekizumab.

The study was sponsored by Janssen Scientific Affairs.

Teeple A, Muser E. Cost per Responder Analysis of Guselkumab Versus Ixekizumab Using Efficacy Results from Long-Term Extension Pivotal Clinical Trials in Patients with Moderate to Severe Plaque Psoriasis. Abstract L17. Presented at the AMCP Nexus 2018, October 22-25, Orlando, FL.
Study Assesses Safety and Efficacy of Novel Nanomicellar Ophthalmic Solution for KCS

OTX-101 0.09% is a novel, aqueous, nanomicellar formulation of cyclosporine that was approved by the FDA to treat keratoconjunctivitis sicca (KCS), an eye condition that is associated with symptoms of burning, stinging, grittiness, and dryness.

Researchers assessed the safety, tolerability, and efficacy of OTX-101 0.09% compared with vehicle when dosed for 84 days in patients with KCS and found that OTX-101 0.09% was superior in increasing tear production and improving corneal and conjunctival staining at 12 weeks. The results of the study were presented at Nexus 2018 during a poster session titled “Phase 3 Clinical Results of Cyclosporine 0.09% in a Novel Nanomicellar Ophthalmic Solution for Treatment of Keratoconjunctivitis Sicca.”

The randomized, multicenter, double-masked, vehicle-controlled, phase 3 study included 744 adult patients with a self-reported history of six months or more of KCS. Patients were randomized 1:1 to receive vehicle (n=373) or OTX-101 0.09% (n=371).

OTX-101 0.09% significantly improved Schirmer’s test scores (primary end-point) compared with vehicle: 16.6% of those receiving OTX-101 0.09% had a 10 mm or more increase in score from baseline to 12 weeks compared with 9.2% of those receiving vehicle ($P<0.0001$).

OTX-101 0.09% also improved conjunctival staining ($-1.54$ vs $-1.15$; $P=0.0007$) and central corneal staining ($-0.30$ vs $-0.24$; $P=0.0159$) compared with vehicle. OTX-101 0.09% improved total corneal staining as early as 28 days after starting treatment ($P=0.0002$). Both treatment options resulted in similar improvements in SANDE scores compared with baseline.

Seventeen patients (4.6%) receiving OTX-101 0.09% experienced adverse events (AEs) compared with three patients (0.8%) receiving vehicle. The most common AEs associated with OTX-101 0.09% were instillation site pain (n=95; 24.2%) and conjunctival hyperemia (n=30; 8.1%).

The study was sponsored by Sun Pharmaceutical Industries.

Luchs J. Phase 3 Clinical Results of Cyclosporine 0.09% in a Novel Nanomicellar Ophthalmic Solution for Treatment of Keratoconjunctivitis Sicca. Abstract 111. Presented at the AMCP Nexus 2018, October 22-25, Orlando, FL.

How Artificial Intelligence Can be Used in Managed Care

Artificial intelligence (AI) uses computer systems to perform tasks that normally require human intelligence, such as visual perception, speech recognition, and decision-making. Machines can receive data sets, categorize them, and learn based on the outcomes.

During a presentation at Nexus 2018, Adam Hanina, chief executive officer at AiCure, and Sam Leo, PharmD, director of specialty clinical programs at Magellan Rx, discussed AI capabilities and how payers can integrate digital solutions in the health system infrastructure to optimize outcomes, reduce costs, and drive better formulary decision-making.

Predictive tools leveraging machine learning can lead to improved forecasting, timely care, and targeted resource utilization with a better focus on preventative treatment. Applications can include personalized formularies, more accurate budget modeling and forecasting, clinical outcome prediction such as adherence, and the development of preventative interventions.

Consumers are increasingly using technology to manage their health (TABLE on next page). There has also been a significant increase in the use of wearable technology (up from 9% in 2014 to 33% in 2018) and health applications (up from 16% in 2014 to 48% in 2018).

All healthcare stakeholders have concerns and perceptions regarding AI:

- Patients ask if it will improve their experience and whether there will be incentives for its use but worry about the “big brother” aspect to this technology.
- Providers consider the acceptance to support the diagnostics and note the need to provide clinicians with additional tools to enhance the ability to treat patients and the need to remove their fear of losing autonomy.
- Organizations ask if it will improve the bottom line and wonder if the technology is validated, accurate, explainable, and compliant. There is also the question of who will support and pay for it.

The speakers provided best practices for incorporating AI:

- Get organized
- Start small
- Carefully evaluate opportunities
- Set clear expectations
- Evaluate, optimize, and grow in a stepwise manner
Depression Severity Associated with Increased Healthcare Costs

Major depressive disorder (MDD) is the second leading cause of disability and is associated with significantly greater work impairment, healthcare resource utilization, and associated costs. Researchers assessed the relationship between The Patient Health Questionnaire-9 (PHQ-9), a validated measure of depression severity, and economic outcomes in a large sample of patients with MDD.

The results of the study were presented at Nexus 2018 during a poster session titled “Relationship Between Patient-Reported Depression Severity Using the Patient Health Questionnaire and Economic Outcomes for Major Depressive Disorder.”

The authors used data from the 2013 U.S. National Health and Wellness Survey, a cross-sectional, internet-based survey that included 75,000 people. Patients were classified with MDD if they had clinician-diagnosed depression and a PHQ-9 score ≥10 or had a PHQ-9 score 0-9 and were taking an antidepressant. Using PHQ-9 interval scores, patients were defined as having no to minimal depression (score, 0-4), mild depression (score, 5-9), moderate depression (score, 10-14), moderately-severe depression (score, 15-19), and severe depression (score, 20-27).

The study included 6,997 patients with MDD: 60.8% were female, 85% were <65 years, and 45.7% were employed. Among this cohort, 344 patients had PHQ-9 scores ≥15 and were receiving two or more concomitant antidepressants.

Compared with those who had no to minimal depression, mean direct medical costs for patients with mild, moderate, moderately-severe, and severe depression were 1.10 (95% confidence interval [CI], 0.92-1.33), 1.28 (95% CI, 1.07-1.58), 1.30 (95% CI, 1.07-1.58), and 1.72 (95% CI, 1.37-2.17) times higher, respectively.

In addition, indirect medical costs for patients with mild, moderate, moderately-severe, and severe depression were 1.62 (95% CI, 1.40-1.89), 2.06 (95% CI, 1.78-2.39), 2.52 (95% CI, 2.13-2.98), and 2.90 (95% CI, 2.35-3.58) times higher, respectively.

Patients with no to minimal depression had lower total costs compared with patients with more severe depression (P<0.05).

“Depression severity measured by PHQ-9 is positively associated with increased direct, indirect, and total costs,” the authors concluded. “These findings suggest that the PHQ-9 is a useful tool to identify patients with MDD.”

The study was sponsored by Janssen Scientific Affairs.

The Future of Managed Care: AMCP Foundation Research Symposium

Nexus 2018 began with the AMCP Foundation 8th Annual Research Symposium, a half-day event that focused on factors that have the potential to disrupt health care and implications if these emerging trends are not addressed.

Following opening remarks, AMCP CEO Susan A. Cantrell, RPh, CAE, chair of the Foundation Board of Trustees, gave a presentation on the future of managed care. “This topic, in particular, is perfectly timed, as we are seeing significant changes and ‘disruptors’ emerge before our eyes,” she said, noting that the industry must be prepared for changes but also involved in shaping the future of managed care.

Ms. Cantrell said AMCP has been focused on the move toward a value-based system that rewards improved outcomes, and although this shift is still in the early stages, it could be a “game changer.”

Other healthcare trends discussed at the symposium included misaligned incentives that drive overutilization of certain treatments, a realization that everyone can’t have everything on demand, and the need to address social determinants to improve patient health. In addition, according to a survey of healthcare stakeholders, drug pricing was identified as having the most impact on the future of health care, with 93% of respondents classifying it as “very or extremely impactful,” followed closely by innovative and curative therapies (88%) and industry consolidation (80%).

“Our symposium each year brings together some of the top experts from across the country to share research and best practices that will help improve the delivery of care,” said Paula J. Eichenbrenner, MBA, CAE, executive director of the AMCP Foundation. “We are proud of this role in supporting the managed care pharmacy profession, which touches the lives of nearly 300 million Americans who are covered under a managed pharmacy benefit.”

“In many ways, managed care pharmacy is at the crossroads of healthcare delivery,” said Ms. Cantrell. “And we’re ideally suited to address many of the emerging changes coming our way.” She noted that while some innovations will make work easier, other disruptors will change the way the industry does business. But either way, it should be about improving patient care, she said.

“Methods of practice are changing not just in managed care pharmacy but also in community and clinical pharmacy,” said Ms. Cantrell. “We are all in this together.”

Managed Care Pharmacy: Preparing for the Future. AMCP Foundation 8th Annual Research Symposium. October 22; Orlando, FL.
A Health Plan’s Take on Innovations in Health Care: Medical Care and the Homeless

During the AMCP Foundation 8th Annual Research Symposium, speakers addressed different stakeholder perspectives on healthcare innovation, including physicians, patients, health plans, and employers. During one of the presentations, Kathy Stillo, MBA, vice president of operations of the clinical redesign team at UnitedHealthcare, represented the health plan perspective and provided an example of a recent innovation.

“Healthcare utilization doesn’t always equal good health,” she said. Sometimes health care is a private, clean, safe residence. Health is impacted by more than clinical performance, including social and economic factors (40%), health behaviors (30%), clinical care (20%), and physical environment (10%).

In an analysis of the data, UnitedHealthcare of Phoenix found that their homeless population use the emergency room (ER) nine times more frequently and are admitted six times more than the average in their Medicaid population. This was leading to three times the cost, despite representing a very small patient base. In this case, just 185 people were driving $2.2 million in medical costs.

So, UnitedHealthcare set up its first housing program in Phoenix. Ms. Stillo provided some member cases of those who were assisted by this intervention.

James is a 50-year-old homeless and unemployed man with chronic kidney disease, gastrointestinal issues, and a serious foot injury. Prior to participating in this housing program, he incurred an average of $18,800 in monthly costs, including 10 hospitalization admissions and one ER visit. After the housing intervention, he incurred an average monthly cost of $1,100, with zero hospital admissions or ER visits.

Alicia is a 31-year-old Medicaid beneficiary who turned to drugs and alcohol and eventually became homeless. She became pregnant and gave birth to a daughter. Following this housing intervention, Alicia became compliant with outpatient treatment and therapy, is 20 months sober, has a job, is enrolled in community college, and is transitioning to permanent housing where she will live independently with her baby.

Among the 41 patients who lived in these housing arrangements for all of 2017, they have observed a 55% reduction in ER visits, a 71% reduction in hospital admissions, and an 81% reduction in hospital days.

The program has housed 119 members through myConnections year to date and plans to house 250 people by the end of the year. By the end of 2019, they project to house 770 members.

“Healthcare utilization doesn’t always equal good health.”

—Kathy Stillo, MBA
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