Supplemental Indications Add Uses, Expand Market

How Payors Can Control Costs
For instance, Humira (adalimumab) was first approved in 2002 for rheumatoid arthritis. Over the years it has obtained nine additional indications, including ankylosing spondylitis, Crohn's disease, and plaque psoriasis. These additional indications have enabled Humira to help several more groups of patients manage their autoimmune diseases, while also making it an ongoing blockbuster for the manufacturer. In 2015, Humira was approved to treat a rare inflammatory skin condition known as hidradenitis suppurativa, for which it received orphan drug status, giving the manufacturer a seven-year market exclusivity for the indication.

Among the many candidates for supplemental indications in the specialty pipeline today are five in late-stage development that could have a potentially large impact on plan sponsors. Two treat prostate cancer, while the other three belong to the important class of drugs that target inflammation via an important signaling protein called interleukin. And all are expected to bring about major clinical change with their new uses.

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Approvals of new drugs may get the headlines. But for patients and payors, it’s just as important when the U.S. Food and Drug Administration (FDA) approves a “supplemental indication” for a drug already on the market — permitting it to be used for new conditions or stages of a disease, or additional patient groups. Such supplemental indications are an important way of expanding the use of medications.

From 2015 to 2017, the FDA approved nearly 140 supplemental indications for specialty drugs.

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Earlier Treatment for Prostate Cancer

In prostate cancer, male hormones called androgens make tumor cells grow, and much of treatment focuses on reducing the amount of androgen produced by the body or in countering its effects. Androgen deprivation therapy (ADT) includes surgically removing the testicles and an array of drugs that either prevent the body from making androgen or block its action. Patients eventually develop resistance to ADT, and the disease continues to spread to other parts of the body. Until recently, after ADT failure, patients had few options beyond chemotherapy with docetaxel.

**Zytiga**

Zytiga (abiraterone), an oral therapy, was originally approved in 2011 for patients who had developed resistance to ADT (patients with castration-resistant prostate cancer), those whose disease had already spread, and those who had already received docetaxel (chemotherapy). Zytiga reduces production of androgen, but unlike other androgen inhibitors, it reduces testosterone production not just in the testicles — which produce the highest levels of androgen — but also in other production sites including the adrenal glands and the prostate tumor itself. In December 2012, the indication was expanded to remove the docetaxel requirement, and in February, to include patients with metastatic prostate cancer who have not received ADT (“castration-sensitive” patients).

**Xtandi**

Xtandi (enzalutamide) has a different method of action. Instead of preventing the production of androgen, it blocks androgen receptors. It was first approved in August 2012 with the same indication as Zytiga: patients with metastatic castration-resistant prostate cancer who have received docetaxel. In September 2014, the indication was expanded to eliminate the docetaxel requirement. Xtandi is pending FDA approval for non-metastatic, castration-resistant prostate cancer and it is in Phase III development for metastatic, castration-sensitive prostate cancer.

Both drugs have been significant additions to the oncologist’s toolbox in their original indications. But there are signs that they may introduce significant change in the treatment of early-stage prostate cancer as well.

In one of the clinical trials supporting its latest indication, Zytiga was associated with a 38 percent reduction in mortality. And preliminary results for Xtandi in non-metastatic prostate cancer, the drug plus ADT reduced the risk of metastasis by 71 percent compared to ADT alone. Both are oral drugs and better tolerated than chemotherapy — an important consideration in a condition that disproportionately affects elderly patients. Zytiga, which costs about $10,000 per month had sales of $1.2 billion in 2017 but faces possible generic competition in the U.S. as early as October, while analysts predict that Xtandi, with a price tag of roughly $7,500 per month, will have sales of $4.7 billion by 2022.
**Targeting New Forms of Inflammation Through Interleukin**

Inflammatory and autoimmune conditions are another therapy class where it has become common for drugs to earn supplemental indications post-launch. Some notable drugs currently pending additional indications include:

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**Dupixent**

Dupixent (dupilumab), a monoclonal antibody (MAb) and interleukin inhibitor, was approved in March 2017 for adult patients with moderate to severe atopic dermatitis. By September, however, Dupixent’s manufacturers reported strong Phase III results in a very different disease: uncontrolled, persistent asthma. The drug reduced the frequency of asthma attacks by 46 percent in the overall group and by 60 to 67 percent in patients with high levels of eosinophils, white blood cells associated with inflammation. The drug could be approved for the new indication as soon as Q4 2018. Meanwhile, clinical trials are also underway to study Dupixent in pediatric atopic dermatitis, nasal polyps, and eosinophilic esophagitis. Dupixent is priced at $37,000 a year, and analysts expect it to achieve peak sales of $2.5 to $4.1 billion from the asthma indication alone.

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**Nucala**

Nucala (mepolizumab), which has a similar mechanism of action as Dupixent, was approved in November 2015 as an add-on treatment for severe eosinophilic asthma. That indication was expanded last December to include eosinophilic granulomatosis with polyangiitis (EGPA), a rare immune condition affecting multiple body systems. The manufacturer has also filed an application for a new indication, as an add-on therapy for severe eosinophilic chronic obstructive pulmonary disease (COPD), based on two Phase III trials.

Use of MAbs for treatment of respiratory disorders is a growing trend and reflects a broader move toward treating asthma as a disease with multiple subtypes, several of which are linked to interleukin and eosinophils. Eosinophilic asthma affects only a small number of patients, but it has long lacked effective treatments. Analysts predict that anti-eosinophilic therapies will make up 19 percent of the COPD drug market by 2025, with Nucala, currently priced at $37,500 a year, leading the pack with $1.2 billion in revenue.

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**Ilaris**

Ilaris (canakinumab), also a MAb, targets interleukin receptor 1β. It was approved in June 2009 to treat cryopyrin-associated periodic syndromes (CAPS), a group of autoinflammatory diseases, then expanded in 2013 to treat systemic juvenile idiopathic arthritis, and expanded again in 2016 to treat three rare periodic fever syndromes. Last August, the manufacturer also presented data on the drug’s effectiveness in reducing the risk of heart attack, stroke, and death due to cardiovascular causes in patients with prior heart attack and inflammatory atherosclerosis, based on a clinical trial that showed a 15 percent reduction in the risk of major cardiovascular events. Analysis of the trial also revealed a surprising finding: a 77 percent reduction in deaths from lung cancer and a 67 percent drop in lung cancer diagnoses among patients receiving the highest doses. The manufacturer plans to conduct a Phase III clinical trial to further explore that finding.

It is too early to know how much impact Ilaris (currently priced at $16,000 a dose, or $200,000 a year) will have on these potential new indications, but it is being hailed for providing evidence that drugs targeting inflammation may eventually play an important role in combating cardiovascular disease, which is responsible for roughly one in four deaths in the U.S.
Targeted Management

In the current landscape, a given dose of a drug is priced the same for all indications regardless of its efficacy in treating each specific condition, or the level of competition in the category. To illustrate, Humira’s cost is the same whether it’s used for rheumatoid arthritis, where there is large amount of longitudinal data available and it competes with 13 other drugs, or for hidradenitis suppurativa, where it’s the only FDA-approved option and there is much less data available. Value-based management strategies like indication-based formularies and rebates can help payors align drug price with the value delivered, by tying formulary placement and reimbursement for a drug to a specific condition rather than negotiating on a therapy class level.

CVS Health monitors the supplemental indication pipeline on an ongoing basis.

For select new drug and supplemental indications we also offer clients Budget Impact Modeling to help them understand the potential impact of these developments on their trend. Our unique integrated specialty management approach offers clients core management strategies that work together for enhanced core management and help reduce spend and trend even more when implemented together.

We constantly develop, implement, and evolve our strategies to help payors stay ahead of market trends.

Formulary: Formulary management is a cornerstone of cost control for payors and is key to managing spend across traditional and specialty therapies. We offer a range of formulary designs that integrate preferred drug, generic maximization and biosimilar strategies. Advanced Control Specialty Formulary offers additional tools such as removals of certain high-cost drugs, control of new products as soon as they launch, and line extensions until they are reviewed for clinical advantages, to further help payors manage costs.

Utilization Management (UM): Our UM programs — such as Specialty Guideline Management, step therapy, and age and disease appropriateness reviews — help ensure that the right drug is being prescribed to the right patient at the right time. Enhanced Specialty Guideline Management — which evaluates each prescription in the context of the patient’s condition and their point in the health care journey — offers even tighter cost control for targeted therapeutic categories. Tools such as new-to-market block, help ensure the right patient gets the right drug at the right time, while creating more opportunities to help manage trend and improve outcomes.

Surya Singh, M.D.
Vice President and Chief Medical Officer, Specialty Pharmacy, CVS Health