FDA Approves OTEZLA® (apremilast) for the Treatment of Oral Ulcers Associated with Behçet’s Disease

OTEZLA reduced the number and pain of oral ulcers in the 12-week placebo-controlled Phase 3 RELIEF™ study

With this third indication in the U.S., OTEZLA is the first and only treatment approved for oral ulcers associated with Behçet’s Disease

SUMMIT, N.J. – (July 19, 2019) — Celgene Corporation (NASDAQ:CELG) today announced that the U.S. Food and Drug Administration (FDA) has approved OTEZLA® (apremilast) 30 mg twice daily (BID) for the treatment of adult patients with oral ulcers associated with Behçet’s Disease. OTEZLA, an oral, selective inhibitor of phosphodiesterase 4 (PDE4), is the first and only approved treatment option for oral ulcers associated with Behçet’s Disease, a rare, chronic, multisystem inflammatory disease that is difficult to treat.

“Oral ulcers are a recurring and debilitating manifestation that affects nearly everyone living with Behçet’s Disease, and have an important negative impact on the quality of life for these patients,” said Yusuf Yazici, M.D., Clinical Associate Professor, Department of Medicine, New York University Langone Health. “In the clinical trial, OTEZLA demonstrated improvements in measures of oral ulcers at week 12. OTEZLA has the potential to be a needed treatment option for U.S. patients and their physicians, who previously had limited options available.”

Behçet’s Disease, also known as Behçet’s Syndrome, affects approximately 5 in 100,000 people in the U.S. Oral ulcers, the most common manifestation of Behçet’s Disease occurring in more than 98% of patients, can be painful, disabling and negatively affect quality of life.

“We are excited to provide the first and only FDA-approved treatment for oral ulcers associated with Behçet’s Disease,” said Terrie Curran, President, Celgene Inflammation & Immunology. “This approval is a reflection of Celgene’s commitment to research in areas of high unmet need, including rare diseases such as Behçet’s Disease. We remain dedicated to further studying OTEZLA and its role in inflammatory conditions.”

The FDA approval was based on efficacy and safety results from the randomized, placebo-controlled, double-blind Phase 3 RELIEF™ study evaluating OTEZLA in 207 adult patients with Behçet’s Disease with active oral ulcers who were previously treated with at least one nonbiologic medication and were candidates for systemic therapy. Results showed OTEZLA 30 mg BID resulted in a 42.7 point reduction from baseline in the pain of oral ulcers as measured by the visual analog scale (VAS) at week 12, compared with an 18.7 point reduction with placebo. The proportion of patients achieving an oral ulcer complete response (oral ulcer-free) at week 12 was 52.9% in the OTEZLA arm and 22.3% in the placebo arm. The
proportion of patients achieving oral ulcer complete response by week 6 and who remained oral ulcer-free for at least six additional weeks during the 12-week treatment phase was 29.8% in the OTEZLA arm and 4.9% in the placebo arm. The daily average number of oral ulcers during the 12-week treatment phase was 1.5 in the OTEZLA arm and 2.6 in the placebo arm (based on oral ulcer counts measured at baseline and at weeks 1, 2, 4, 6, 8, 10 and 12).

“Behçet’s Disease is a chronic inflammatory disease in which patients present with symptoms such as oral ulcers that can have a significant impact on daily life,” said Mirta Avila Santos, M.D., Executive Director, American Behçet’s Disease Association. “Today’s approval for OTEZLA marks an important milestone for people with Behçet’s Disease who have been eagerly waiting for treatment options for their oral ulcers.”

The most common adverse events observed occurring in ≥10% of patients in the RELIEF trial were diarrhea (41.3% with OTEZLA; 20.4% for placebo), nausea (19.2% with OTEZLA; 10.7% for placebo), headache (14.4% with OTEZLA; 10.7% for placebo) and upper respiratory tract infection (11.5% with OTEZLA; 4.9% for placebo). The safety profile was consistent with the known safety profile of OTEZLA.

OTEZLA is now approved for three indications in the U.S., including the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, adult patients with active psoriatic arthritis and adult patients with oral ulcers associated with Behçet’s Disease. Since its initial FDA approval in 2014, OTEZLA has been prescribed to more than 250,000 patients with moderate to severe plaque psoriasis or active psoriatic arthritis in the U.S.4

OTEZLA is available in the U.S. and is dispensed through a comprehensive network of specialty pharmacies. For more information about accessing OTEZLA and patient support services (including reimbursement assistance and 24/7 nurse support), doctors and patients can contact OTEZLA® SupportPlus™ at 1-844-4OTEZLA (1-844-468-3952) or visit www.OTEZLA.com for more information.

Celgene anticipates a regulatory decision for OTEZLA in oral ulcers associated with Behçet’s Disease from the Pharmaceuticals and Medical Devices Agency in Japan in the second half of 2019. The Company also submitted a Type II Variation to the Marketing Authorization Application earlier this year seeking approval in the European Union.

About the RELIEF™ Study
The RELIEF™ study is a Phase 3 randomized, placebo-controlled, double-blind study evaluating OTEZLA 30 mg BID in 207 adult patients with Behçet’s Disease with active oral ulcers who were previously treated with at least one nonbiologic medication and were candidates for systemic therapy. This 64-week study was conducted at 53 sites across 10 countries.

In the study, 207 adult patients were randomized 1:1 to receive either OTEZLA 30 mg BID (n=104) or placebo (n=103) for the 12-week placebo-controlled treatment phase. Upon completion of week 12, all patients received OTEZLA for the 52-week active treatment phase. Efficacy was assessed based on the number and pain of oral ulcers, including the daily average number of oral ulcers during the 12-week placebo-controlled treatment phase.

About Behçet’s Disease
Behçet’s Disease is associated with abnormalities of the immune system and inflammation of the blood vessels. Behçet’s Disease is characterized by recurrent oral and genital ulcers, skin lesions, uveitis,
arthritis, vascular, central nervous system and gastrointestinal involvement. Oral ulcers are present in more than 98% of Behçet’s Disease patients.

Behçet’s Disease has been classified in the U.S. as a rare or “orphan” disease by the National Institutes of Health. At this time, there are limited approved therapies to treat Behçet’s Disease in the U.S. Prevalence of Behçet’s Disease is highest in the Middle East, Asia and Japan.

About OTEZLA® (apremilast)
OTEZLA® (apremilast) 30 mg tablets is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, which is thought to indirectly modulate the production of inflammatory mediators. The specific mechanism(s) by which OTEZLA exerts its therapeutic action in patients is not well defined.

U.S. PRESCRIBING INFORMATION

INDICATIONS
Otezla® (apremilast) is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.

Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet’s Disease.

IMPORTANT SAFETY INFORMATION
Contraindications
Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.

Warnings and Precautions
Diarrhea, Nausea and Vomiting: Cases of severe diarrhea, nausea, and vomiting were associated with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Depression: Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur.

Psoriasis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.3% (12/920) of patients reported depression compared to 0.4% (2/506) on placebo. Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide.
Psoriatic Arthritis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.0% (10/998) reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. Suicidal ideation and behavior was observed in 0.2% (3/1441) of patients on Otezla, compared to none in placebo-treated patients. Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo-treated patients (0/495). Two patients who received placebo committed suicide compared to none on Otezla.

Behçet’s Disease: Treatment with Otezla is associated with an increase in depression. During the clinical trial, 1% (1/104) reported depression or depressed mood compared to 1% (1/103) treated with placebo. No instances of suicidal ideation or behavior were reported in patients treated with Otezla or treated with placebo.

Weight Decrease: Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla

Psoriasis: Body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) of patients treated with placebo.

Psoriatic Arthritis: Body weight loss of 5-10% was reported in 10% (49/497) of patients taking Otezla and in 3.3% (16/495) of patients taking placebo.

Behçet’s Disease: Body weight loss of >5% was reported in 4.9% (5/103) of patients taking Otezla and in 3.9% (4/102) of patients taking placebo.

Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.

Adverse Reactions

Psoriasis: Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)

Psoriatic Arthritis: Adverse reactions reported in at least 2% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 16 weeks (after the initial 5-day titration), were (Otezla%, placebo%): diarrhea (7.7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2)

Behçet’s Disease: Adverse reactions reported in at least ≥5% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 12 weeks were (Otezla%, placebo%): diarrhea (41.3, 20.4); nausea (19.2, 10.7); headache (14.4, 10.7); upper respiratory tract infection (11.5, 4.9); upper abdominal pain (8.7, 1.9); vomiting (8.7, 1.9); back pain (7.7, 5.8); viral upper respiratory tract infection (6.7, 4.9); arthralgia (5.8, 2.9).

Use in Specific Populations
Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Otezla during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/.

Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition.

Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information.

Please click here for Full Prescribing Information.

About Celgene
Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global pharmaceutical company engaged primarily in the discovery, development and commercialization of innovative therapies for the treatment of cancer and inflammatory diseases through next-generation solutions in protein homeostasis, immuno-oncology, epigenetics, immunology and neuro-inflammation. For more information, please visit www.celgene.com. Follow Celgene on Social Media: @Celgene, Pinterest, LinkedIn, Facebook and YouTube.

Forward-Looking Statements
This press release contains forward-looking statements, which are generally statements that are not historical facts. Forward-looking statements can be identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans," "will," "outlook" and similar expressions. Forward-looking statements are based on management's current plans, estimates, assumptions and projections, and speak only as of the date they are made. We undertake no obligation to update any forward-looking statement in light of new information or future events, except as otherwise required by law. Forward-looking statements involve inherent risks and uncertainties, most of which are difficult to predict and are generally beyond our control. Actual results or outcomes may differ materially from those implied by the forward-looking statements as a result of the impact of a number of factors, many of which are discussed in more detail in our Annual Report on Form 10-K and our other reports filed with the U.S. Securities and Exchange Commission, including factors related to the proposed transaction between Bristol-Myers Squibb and Celgene, such as, but not limited to, the risks that: management’s time and attention is diverted on transaction related issues; disruption from the transaction make it more difficult to maintain business, contractual and operational relationships; legal proceedings are instituted against Bristol-Myers Squibb, Celgene or the combined company that could delay or prevent the proposed transaction; and Bristol-Myers Squibb, Celgene or the combined company is unable to retain key personnel.

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4 Symphony Health Solution PrescriberSource PatientFocus, Includes all prescriptions from April 2014 through April 2019.