Celgene Receives Positive CHMP Opinion for OTEZLA® (apremilast), the First Oral PDE4 Inhibitor for the Treatment of Patients with Psoriasis and Psoriatic Arthritis

BOUDRY, Switzerland--(BUSINESS WIRE)-- Celgene International Sàrl (NASDAQ: CELG), a wholly-owned subsidiary of Celgene Corporation, today announced that the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for OTEZLA® (apremilast), the Company’s oral selective inhibitor of phosphodiesterase 4 (PDE4), in two therapeutic indications:

- For the treatment of moderate-to-severe chronic plaque psoriasis in adult patients who failed to respond to or, who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).
- Alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Psoriasis is an immune mediated skin condition characterised by raised scaly lesions on the skin. It affects approximately 14 million people across Europe and about 125 million people worldwide. Plaque psoriasis, also called psoriasis vulgaris, is the most common form of the disease, representing about 80 percent of cases. Up to 30 percent of people with psoriasis may develop psoriatic arthritis, which involves pain and swelling in joints and other manifestations and may lead to significant disability.

“This CHMP positive opinion is an important step forward for people with psoriasis and psoriatic arthritis in Europe. These immune mediated diseases are frequently debilitating and cause severe physical and emotional pain to the individual,” stated Tuomo Pätsi, President, Celgene Europe, the Middle East and Africa (EMEA). “We are proud to have moved one step closer to offering patients OTEZLA®, a new, oral treatment approach that could significantly help control their symptoms and make a considerable difference to their quality of life.”

In the ESTEEM studies, which form the basis of CHMP’s positive opinion for apremilast in psoriasis, treatment resulted in significant and clinically meaningful improvements in plaque psoriasis as measured by PASI-75 (a 75 percent improvement in the Psoriasis Area Severity Index) scores at week 16, the primary endpoint. Patients on apremilast also benefited from significant improvements in difficult to treat areas, such as nail and scalp, and itch, known to have a marked impact on patients' quality of life and perception of disease severity.

In the PALACE program, which forms the basis for CHMP’s positive opinion for apremilast in psoriatic arthritis, treatment resulted in significant and clinically meaningful improvements in the signs and symptoms of psoriatic arthritis, as measured by the modified ACR-20 (a 20 percent improvement in the American College of Rheumatology disease activity criteria) response at 16 weeks, the primary endpoint. Patients on apremilast showed improvement across multiple disease manifestations specific to psoriatic arthritis, such as swollen and tender joints, as well as dactylitis, enthesitis and overall physical function.

In the two Phase III programs, PALACE and ESTEEM, the clinical response of OTEZLA was maintained through week 52 across multiple endpoints.

Across these phase III clinical studies, the most commonly reported adverse reactions were consistently diarrhoea, nausea, upper respiratory tract infection, tension headache and headache. These adverse reactions were mostly mild to moderate in severity. Gastrointestinal adverse reactions generally occurred within the first two weeks of treatment and usually resolved within four weeks. During the placebo-controlled phase of the clinical trials, the rate of major adverse cardiac events, serious infections, including opportunistic infections, and malignancies, was comparable between placebo and apremilast groups.
OTEZLA® was approved on March 21, 2014 by the U.S. Food and Drug Administration (FDA) for the treatment of adults with active psoriatic arthritis and on September 23, 2014 for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. In Canada, OTEZLA was approved for the treatment of moderate-to-severe plaque psoriasis in November 2014. A New Drug Submission (NDS) for psoriatic arthritis was submitted to Canadian Health Authorities in the second quarter of 2013. Marketing authorisation applications are ongoing in other countries, including Australia and Switzerland.

The European Commission, which generally follows the recommendation of the CHMP, is expected to make its final decision within two to three months. If approval is granted, detailed conditions for the use of this product will be described in the Summary of Product Characteristics (SmPC), which will be published in the revised European Public Assessment Report (EPAR).

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Note to editors: Additional information can be found at: http://smp.businesswire.com/pages/celgene-receives-positive-chmp-opinion-otezla-apremilast-first-oral-pde4-inhibitor-treatment

About OTEZLA®

OTEZLA® is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic AMP (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 with psoriasis or psoriatic arthritis is not well defined.17 Find out more about PDE4 inhibition, by clicking here: http://discoverpde4.com/

About ESTEEM 1 and 2

ESTEEM 1 and 2 are two large pivotal phase III randomized, placebo-controlled studies evaluating apremilast in patients with a diagnosis of moderate to severe plaque psoriasis for at least 12 months prior to screening, and who were also candidates for phototherapy or systemic therapy. Approximately 1,250 patients were randomized 2:1 to receive either apremilast 30 mg twice daily or placebo after an initial five-day titration period, for the first 16 weeks, followed by a maintenance phase from weeks 16-32 in which placebo patients were switched to apremilast 30 mg twice daily through week 32, and a randomized withdrawal phase for responders from week 32 to week 52 based on their initial apremilast randomization and Psoriasis Area and Severity Index (PASI) response. Approximately 30 percent of all patients had received prior phototherapy and 54 percent had received prior conventional systemic and/or biologic therapy.

About PALACE Program

PALACE 1, 2 and 3 are three pivotal phase III multi-center, double-blind, placebo-controlled, parallel-group studies with two active-treatment groups. Across these studies, approximately 1,500 patients were randomized 1:1:1 to receive either apremilast 20 mg twice daily, apremilast 30 mg twice daily or identically-appearing placebo, for 16 weeks. At week 16, some placebo-treated patients were randomized to one of the two apremilast groups, while others remained on placebo through week 24. After week 24, patients began a subsequent long term, open-label, active treatment phase. The PALACE 1, 2 and 3 studies included a wide spectrum of patients with active psoriatic arthritis, who had been previously treated with oral disease-modifying anti rheumatic drugs (DMARDs), and/or biologics, with some patients who had previously failed a tumour necrosis factor (TNF) blocker. Taken together, the PALACE program is the largest psoriatic arthritis program to date intended for regulatory submission.

ADDITIONAL IMPORTANT SAFETY INFORMATION based on US label

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

Depression: Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behaviour, 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 adverse reactions of depression. During clinical trials, 1.3%
(12/920) of patients treated with Otezla® reported depression compared to 2.0% (2/227) of patients treated with placebo; 0.1% (1/1308) of patients discontinued treatment due to depression compared with none on placebo (0/227). Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla®, compared to none in placebo-treated patients (0/227). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla®, compared to none (0/1308) on placebo. One patient treated with Otezla® attempted suicide; one patient on placebo died by suicide.

Psoriatic Arthritis: During clinical trials, 1.0% (10/998) of patients treated with Otezla reported depression or depressed mood compared to 0.8% (4/495) treated with placebo; 0.3% (4/1441) of patients treated with Otezla® discontinued treatment due to depression or depressed mood compared with none in placebo treated patients (0/495). Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo treated patients (0/495). Suicidal ideation and behavior were observed in 0.2% (3/1441) of patients on Otezla, compared to none on placebo (0/495). Two patients who received placebo committed suicide compared to none on Otezla.

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% of patients taking Otezla and in 3.3% of patients taking placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla.

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 (eg, 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 ≥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).

Use in Specific Populations

Pregnancy and Nursing Mothers: Otezla is Pregnancy Category C; it has not been studied in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether apremilast or its metabolites are present in human milk. Caution should be exercised when Otezla is administered to a nursing woman.

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 (USA Label)

About Psoriasis

Psoriasis is an immune-mediated, non-contagious, inflammatory skin disorder of unknown cause. The disorder is a chronic recurring condition which varies in severity from minor localised patches to complete body coverage. Plaque psoriasis is the most common type of psoriasis. About 80 percent of people who develop psoriasis have plaque psoriasis, which appears as patches of raised, reddish skin covered by silvery-white scales. These patches, or plaques, frequently form on the elbows, knees, lower back, and scalp. Psoriasis occurs nearly equally in males and females and it affects many aspects of patients' emotional and social well-being as well as daily activities and the ability to study or work. In May 2014, the 67th World Health Assembly adopted a resolution on psoriasis encouraging Member States to engage further in advocacy efforts to raise awareness of the disease and to fight stigmatisation among people living with the condition.

About Psoriatic Arthritis
Psoriatic arthritis is a painful, chronic inflammatory disease characterised by pain, stiffness, swelling and tenderness of the joints, inflammation of specific ligaments and tendons, and decrease in physical functioning.\textsuperscript{20} It is estimated that nearly 38 million people worldwide have psoriatic arthritis.\textsuperscript{21,22} Psoriatic arthritis can impact the ability to perform day-to-day activities and has been reported to increase work disability. Enthesitis (inflammation at sites where tendons or ligaments insert into bone) and dactylitis (inflammation of fingers and toes, commonly known as “sausage fingers”) are specific disease manifestations related to psoriatic arthritis.\textsuperscript{20}

About Celgene

Celgene International Sàrl, located in Boudry, in the Canton of Neuchâtel, Switzerland, is a wholly-owned subsidiary and International Headquarters of Celgene Corporation. 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 gene and protein regulation. For more information, please visit the Company's website at \texttt{www.celgene.com}. Follow Celgene on Twitter @ Celgene.

Forward-Looking Statements

\textit{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 other reports filed with the Securities and Exchange Commission.}

References

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