 Celgene Receives CHMP Positive Opinions for Both REVLIMID® (lenalidomide) and IMNOVID® (pomalidomide)-Based Triplet Combination Regimens for Patients with Multiple Myeloma

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The CHMP adopted two positive opinions recommending European Commission approval of:

- REVLIMID in combination with bortezomib and dexamethasone (RVd) in adult patients with previously untreated multiple myeloma who are not eligible for transplant
- IMNOVID in combination with bortezomib and dexamethasone (Pvd), for adult patients with multiple myeloma, who have received at least one prior treatment regimen including lenalidomide

SUMMIT, N.J.-(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG), today announced that the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) has adopted positive opinions for two triplet regimens based on Celgene’s proprietary IMiD® medications, REVLIMID (lenalidomide) and IMNOVID (pomalidomide).

The CHMP recommended approval of an expanded indication of REVLIMID as combination therapy with bortezomib and dexamethasone (RVd) for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

The committee also recommended approval of IMNOVID in combination with bortezomib and dexamethasone...
(PVD), for the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

The European Commission, which generally follows the recommendation of the CHMP, is expected to make its final decision in approximately two months.

“The CHMP positive opinions for our IMiD combinations, RVd and PVd represent very good news for patients with multiple myeloma in Europe,” said Nadim Ahmed, President, Hematology/Oncology for Celgene. “We look forward to potential EMA approvals, which would make these new triplet regimens available to patients, as we aim to improve patient outcomes across multiple stages of their disease.”

The CHMP positive opinion for REVLIMID was based on the data from SWOG S0777, a phase 3 trial evaluating the triplet combination of REVLIMID, bortezomib and dexamethasone (RVd) in adult patients with previously untreated multiple myeloma, without an intent for immediate autologous stem cell transplant (ASCT).1 Results from SWOG S0777 showed statistically significant progression-free (PFS) and overall survival improvements in patients treated with RVd compared to those treated with REVLIMID and dexamethasone alone (Rd). The choice of treatment in a first-line therapy setting is important2 as patients progressively become less responsive to therapy and experience shorter periods of remission at later lines of treatment.3

The CHMP positive opinion for PVd was based on the data from OPTIMISM MM, the first prospective phase 3 trial to evaluate an IMNOVID-based triplet regimen in patients who were previously treated with REVLIMID, and who were, in the majority (70 percent), REVLIMID refractory.4 This patient population represents a growing unmet medical need for which new treatment options are necessary. Results from OPTIMISM MM showed that patients receiving PVd achieved a significantly longer PFS than those in the Vd treatment arm.

REVLIMID in combination with bortezomib and dexamethasone and IMNOVID in combination with bortezomib and dexamethasone are not approved for any use in any country.

About Celgene’s Immunomodulatory Drugs

IMiD® agents are Celgene’s proprietary small molecule, orally available compounds for the treatment of some blood cancers. IMiD agents are hypothesized to have multiple mechanisms of action. They have been found to increase activation and proliferation of T cells, and proliferation of the IL-2 protein and activity of CD8+ effector T cells. IMiD agents have also been found to affect the stimulation and expression of natural killer (NK) cells, working within the environment of the cell to stimulate the immune system to attack the cancer cells, as well as attack the cancer cells directly. In addition to immunomodulatory properties, IMiD agents are hypothesized to have tumoricidal and antiangiogenic activity. Celgene’s portfolio of IMiD agents have become a foundation of multiple
myeloma research, with a growing number of studies exploring these compounds as combination partners across a range of settings of the disease.

About Multiple Myeloma

Multiple myeloma is a life-threatening blood cancer that is characterized by tumor proliferation and suppression of the immune system. It is a rare but deadly disease—around 42,000 people are diagnosed with multiple myeloma in Europe, and approximately 26,000 people die from the disease each year. The typical multiple myeloma disease course includes periods of symptomatic myeloma followed by periods of remission, and eventually, the disease becomes refractory (nonresponsive).

About SWOG S0777

SWOG S0777 is a randomized, open-label, multicentre, phase 3 study aiming to evaluate the efficacy and safety of RVd compared to Rd in treating patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT).

SWOG S0777 recruited 525 patients with symptomatic and measurable ndMM aged 18 years and older. Patients were randomly assigned (1:1) to receive either an initial treatment of lenalidomide with bortezomib and dexamethasone (RVd group) or lenalidomide and dexamethasone alone (Rd group). Randomization was stratified based on International Staging System stage (I, II, or III) and intent to transplant (yes versus no). The RVd regimen was given as eight 21-day cycles. Bortezomib was given at 1.3 mg/m² intravenously on days 1, 4, 8, and 11, combined with oral lenalidomide 25 mg daily on days 1-14 plus oral dexamethasone 20 mg daily on days 1, 2, 4, 5, 8, 9, 11, and 12. The Rd regimen was given as six 28-day cycles. The standard Rd regimen consisted of 25 mg oral lenalidomide once a day for days 1-21 plus 40 mg oral dexamethasone once a day on days 1, 8, 15, and 22.

Results from SWOG S0777 showed that median progression-free survival (PFS) was significantly improved in patients receiving RVd compared to those receiving REVLIMID and dexamethasone (Rd) alone (42 months versus 30 months; HR 0.76, 95% CI 0.62-0.94; P=0.01). Median overall survival was also significantly improved in patients receiving RVd compared to those receiving Rd (89 months versus 67 months; HR 0.72, 95% CI 0.56–0.94; P=0.013). The rates of overall and complete response were higher in those receiving RVd compared to Rd (overall response: 82% RVd vs 72% Rd; complete response: 16% RVd vs 8% Rd). The safety of RVd was also consistent with the well-established safety profiles of each drug in the triplet therapy.

Upon completion of induction, all patients received ongoing maintenance with 25 mg oral lenalidomide once a day for 21 days plus 40 mg oral dexamethasone once a day for days 1, 8, 15, and 22 of each 28-day cycle.
About OPTIMISMM

OPTIMISMM is the first phase 3 trial designed to compare the safety and efficacy of PVd versus Vd, as an early line of therapy in patients with relapsed and refractory multiple myeloma (with 1-3 prior regimens of therapy) and prior REVLIMID-exposure, including REVLIMID-refractory patients.

The multi-center, international, open-label, randomized phase 3 clinical trial included 559 patients (281 patients in the PVd arm and 278 in the Vd arm). Demographic, baseline, and prior disease characteristics were generally well balanced between the two treatment arms. The median number of prior lines of therapy was two, while more than one third had one prior line of treatment (40% across both treatment arms). All patients had prior treatment with REVLIMID® with the majority being REVLIMID refractory (71 percent in the PVd arm vs 69 percent in the Vd arm) and 70 percent vs 66 percent, respectively, were refractory to their last treatment. Median follow-up was 16 months.

Results from OPTIMISMM showed that patients receiving PVd achieved a significantly longer PFS than those in the Vd treatment arm (11.20 months vs. 7.10 months, respectively [P= < .0001, HR 0.61; 95% CI: (0.49-0.77)], reducing the risk of disease progression or death by 39% in the PVd arm. In an exploratory sub-group analysis of patients with one prior line of therapy, median progression-free survival with PVd was 20.73 months vs 11.63 months with Vd (HR 0.54; p=0·0027). In these patients, the benefit of PVd was independent of whether they were refractory or non-refractory to prior therapy with lenalidomide. The safety of PVd was consistent with the well-established safety profiles of each drug in the triplet therapy.

Patients were stratified based on age (≤ 75 years old vs > 75 years old), number of prior anti-myeloma regimens (1 vs. > 1), and β2-microglobulin levels (< 3.5 mg/L vs ≥ 3.5 to ≤ 5.5 mg/L vs > 5.5 mg/L). Patients were randomized 1:1 to receive PVd or Vd. In 21-day cycles, patients received IMNOVID 4 mg/d on days 1-14 (PVd arm only); bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11 of cycles 1-8 and on days 1 and 8 of cycles 9 and beyond; and dexamethasone 20 mg/d (10 mg if aged > 75 years) on the days of and after receiving bortezomib treatment.

About REVLIMID®

REVLIMID® (lenalidomide) in combination with dexamethasone (dex) is indicated for the treatment of patients with multiple myeloma (MM)

REVLIMID is indicated as maintenance therapy in patients with MM following autologous hematopoietic stem cell transplantation (auto-HSCT)
REVLIMID® is indicated for the treatment of patients with transfusion-dependent anemia due to low-or intermediate-1–risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

REVLIMID® is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib

REVLIMID is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS® program.

Information about the REVLIMID REMS® program is available at www.celgeneriskmanagement.com or by calling the manufacturer’s toll-free number 1-888-423-5436.

Hematologic Toxicity (Neutropenia and Thrombocytopenia)

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay/reduction during the major study. Thirty-four
percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

Venous and Arterial Thromboembolism

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with MM who were treated with REVLIMID and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

CONTRAINDICATIONS

Pregnancy: REVLIMID can cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus

Severe Hypersensitivity Reactions: REVLIMID is contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: See Boxed WARNINGS

- Females of Reproductive Potential: See Boxed WARNINGS
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 4 weeks after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must
not be exposed to REVLIMID

REVLIMID REMS ® Program: See Boxed WARNINGS: Prescribers and pharmacies must be certified with the REVLIMID REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive REVLIMID. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

Hematologic Toxicity: REVLIMID can cause significant neutropenia and thrombocytopenia. Monitor patients with neutropenia for signs of infection. Advise patients to observe for bleeding or bruising, especially with use of concomitant medications that may increase risk of bleeding. MM: Patients taking REVLIMID/dex or REVLIMID as maintenance therapy should have their complete blood counts (CBC) assessed every 7 days for the first 2 cycles, on days 1 and 15 of cycle 3, and every 28 days thereafter. MDS: Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or dose reduction. Please see the Black Box WARNINGS for further information. MCL: Patients taking REVLIMID for MCL should have their CBCs monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction.

Venous and Arterial Thromboembolism: See Boxed WARNINGS: Venous thromboembolic events (DVT and PE) and arterial thromboses (MI and CVA) are increased in patients treated with REVLIMID. Patients with known risk factors, including prior thrombosis, may be at greater risk and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended and the regimen should be based on patient’s underlying risks. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision.

Increased Mortality in Patients with CLL: In a clinical trial in the first-line treatment of patients with CLL, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in the REVLIMID arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Second Primary Malignancies (SPM): In clinical trials in patients with MM receiving REVLIMID, an increase of hematologic plus solid tumor SPM, notably AML and MDS, have been observed. Monitor patients for the development of SPM. Take into account both the potential benefit of REVLIMID and risk of SPM when considering treatment.
Increased Mortality with Pembrolizumab: In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with REVLIMID/dex. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Severe Cutaneous Reactions Including Hypersensitivity Reactions: Angioedema and severe cutaneous reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash, or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN, or DRESS is suspected and should not be resumed following discontinuation for these reactions.

Tumor Lysis Syndrome (TLS): Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Tumor Flare Reaction (TFR): TFR has occurred during investigational use of lenalidomide for CLL and lymphoma. Monitoring and evaluation for TFR is recommended in patients with MCL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with REVLIMID until TFR resolves to ≤ Grade 1. REVLIMID may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion.

Impaired Stem Cell Mobilization: A decrease in the number of CD34+ cells collected after treatment (>4 cycles) with REVLIMID has been reported. Consider early referral to transplant center to optimize timing of the stem cell collection.

Thyroid Disorders: Both hypothyroidism and hyperthyroidism have been reported. Measure thyroid function.
before start of REVLIMID treatment and during therapy

**Early Mortality in Patients with MCL:** In another MCL study, there was an increase in early deaths (within 20 weeks), 12.9% in the REVLIMID arm versus 7.1% in the control arm. Risk factors for early deaths include high tumor burden, MIPI score at diagnosis, and high WBC at baseline (≥10 x 10^9/L)

**ADVERSE REACTIONS**

**Multiple Myeloma**

- In newly diagnosed: The most frequently reported Grade 3 or 4 reactions included neutropenia, anemia, thrombocytopenia, pneumonia, asthenia, fatigue, back pain, hypokalemia, rash, cataract, lymphopenia, dyspnea, DVT, hyperglycemia, and leukopenia. The highest frequency of infections occurred in Arm Rd Continuous (75%) compared to Arm MPT (56%). There were more Grade 3 and 4 and serious adverse reactions of infection in Arm Rd Continuous than either Arm MPT or Rd18

- The most common adverse reactions reported in ≥20% (Arm Rd Continuous): diarrhea (46%), anemia (44%), neutropenia (35%), fatigue (33%), back pain (32%), asthenia (28%), insomnia (28%), rash (26%), decreased appetite (23%), cough (23%), dyspnea (22%), pyrexia (21%), abdominal pain (21%), muscle spasms (20%), and thrombocytopenia (20%)

- Maintenance Therapy Post Auto-HSCT: The most frequently reported Grade 3 or 4 reactions in ≥20% (REVLIMID arm) included neutropenia, thrombocytopenia, and leukopenia. The serious adverse reactions of lung infection and neutropenia (more than 4.5%) occurred in the REVLIMID arm

- The most frequently reported adverse reactions in ≥20% (REVLIMID arm) across both maintenance studies (Study 1, Study 2) were neutropenia (79%, 61%), thrombocytopenia (72%, 24%), leukopenia (23%, 32%), anemia (21%, 9%), upper respiratory tract infection (27%, 11%), bronchitis (5%, 47%), nasopharyngitis (2%, 35%), cough (10%, 27%), gastroenteritis (0%, 23%), diarrhea (55%, 39%), rash (32%, 8%), fatigue (23%, 11%), asthenia (0%, 30%), muscle spasm (0%, 33%), and pyrexia (8%, 21%)

- After at least one prior therapy: The most common adverse reactions reported in ≥20% (REVLIMID/dex vs dex/placebo): fatigue (44% vs 42%), neutropenia (42% vs 6%), constipation (41% vs 21%), diarrhea (39% vs 27%), muscle cramp (33% vs 21%), anemia (31% vs 24%), pyrexia (28% vs 23%), peripheral edema (26% vs 21%), nausea (26% vs 21%), back pain (26% vs 19%), upper respiratory tract infection (25% vs 16%), dyspnea (24% vs 17%), dizziness (23% vs 17%), thrombocytopenia (22% vs 11%), rash (21% vs 9%), tremor (21% vs 7%), and weight decreased (20% vs 15%)

**Myelodysplastic Syndromes**
Grade 3 and 4 adverse events reported in ≥ 5% of patients with del 5q MDS were neutropenia (53%), thrombocytopenia (50%), pneumonia (7%), rash (7%), anemia (6%), leukopenia (5%), fatigue (5%), dyspnea (5%), and back pain (5%).

Adverse events reported in ≥15% of del 5q MDS patients (REVLIMID): thrombocytopenia (61.5%), neutropenia (58.8%), diarrhea (49%), pruritus (42%), rash (36%), fatigue (31%), constipation (24%), nausea (24%), nasopharyngitis (23%), arthralgia (22%), pyrexia (21%), back pain (21%), peripheral edema (20%), cough (20%), dizziness (20%), headache (20%), muscle cramp (18%), dyspnea (17%), pharyngitis (16%), epistaxis (15%), asthenia (15%), upper respiratory tract infection (15%)

**Mantle Cell Lymphoma**

- Grade 3 and 4 adverse events reported in ≥5% of patients treated with REVLIMID in the MCL trial (N=134) included neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), leukopenia (7%), fatigue (7%), diarrhea (6%), dyspnea (6%), and febrile neutropenia (6%).
- Adverse events reported in ≥15% of patients treated with REVLIMID in the MCL trial included neutropenia (49%), thrombocytopenia (36%), fatigue (34%), anemia (31%), diarrhea (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritus (17%), peripheral edema (16%), constipation (16%), and leukopenia (15%).

**DRUG INTERACTIONS**

Periodic monitoring of digoxin plasma levels is recommended due to increased Cmax and AUC with concomitant REVLIMID therapy. Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thrombosis. It is not known whether there is an interaction between dex and warfarin. Close monitoring of PT and INR is recommended in patients with MM taking concomitant warfarin.

**USE IN SPECIFIC POPULATIONS**

- **PREGNANCY:** See Boxed WARNINGS: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a REVLIMID pregnancy exposure registry that monitors pregnancy outcomes in females exposed to REVLIMID during pregnancy as well as female partners of male patients who are exposed to REVLIMID. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to REVLIMID to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.
- LACTATION: There is no information regarding the presence of lenalidomide in human milk, the effects of REVLIMID on the breastfed infant, or the effects of REVLIMID on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from REVLIMID, advise female patients not to breastfeed during treatment with REVLIMID.

- PEDIATRIC USE: Safety and effectiveness have not been established in pediatric patients.

- RENAL IMPAIRMENT: Adjust the starting dose of REVLIMID based on the creatinine clearance value and in patients on dialysis.

Please see full Prescribing Information, including Boxed WARNINGS.

About IMNOVID ® (pomalidomide)

IMNOVID® in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. It belongs to a group of drugs called immunomodulatory drugs (IMiDs®).

IMNOVID, which is marketed under trade name POMALYST® in the US, was first approved for use in the US in 2013 in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Imnovid in combination with bortezomib and dexamethasone is not approved for use in United States.

It was approved in the EU in 2013, in combination with dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

It is also approved in a total of 66 countries worldwide including Australia, Canada, Japan and Switzerland for use in combination with dexamethasone for similar indications to US and EU.

About POMALYST

Indication

POMALYST® (pomalidomide) is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome...
inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity
- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.
- Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.

POMALYST is only available through a restricted distribution program called POMALYST REMS ®.

Venous and Arterial Thromboembolism
- Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.

CONTRAINDICATIONS

- **Pregnancy**: POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If POMALYST is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus.

WARNINGS AND PRECAUTIONS

- **Embryo-Fetal Toxicity & Females of Reproductive Potential**: See Boxed WARNINGS
- **Males**: Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 4 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm.
- **Blood Donation**: Patients must not donate blood during treatment with POMALYST and for 4 weeks following discontinuation of POMALYST therapy because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.
- **POMALYST REMS ® Program**: See Boxed WARNINGS
- Prescribers and pharmacies must be certified with the POMALYST REMS program by enrolling and complying with the REMS requirements; pharmacies must only dispense to patients who are authorized to receive
POMALYST. Patients must sign a Patient-Physician Agreement Form and comply with REMS requirements; female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.

- Further information about the POMALYST REMS program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

- Venous and Arterial Thromboembolism: See Boxed WARNINGS. Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient’s underlying risk factors.

- Increased Mortality with Pembrolizumab: In clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

- Hematologic Toxicity: Neutropenia (46%) was the most frequently reported Grade 3/4 adverse reaction in patients taking POMALYST in clinical trials, followed by anemia and thrombocytopenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification.

- Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor liver function tests monthly. Stop POMALYST upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

- Severe Cutaneous Reactions Including Hypersensitivity Reactions: Angioedema and severe cutaneous reactions including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Discontinue POMALYST for angioedema, skin exfoliation, bullae, or any other severe cutaneous reactions such as SJS, TEN or DRESS, and do not resume therapy.

- Dizziness and Confusional State: In patients taking POMALYST in clinical trials, 14% experienced dizziness (1% Grade 3 or 4) and 7% a confusional state (3% Grade 3 or 4). Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.
Neuropathy: In patients taking POMALYST in clinical trials, 18% experienced neuropathy (2% Grade 3 in one trial) and 12% peripheral neuropathy.

Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

Tumor Lysis Syndrome (TLS): TLS may occur in patients treated with POMALYST. Patients at risk are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

ADVERSE REACTIONS

The most common adverse reactions for POMALYST (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain, and pyrexia.

In the phase III trial, nearly all patients treated with POMALYST + low-dose dex experienced at least one adverse reaction (99%). Adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥2% higher than control) included neutropenia (51.3%), fatigue and asthenia (46.7%), upper respiratory tract infection (31%), thrombocytopenia (29.7%), pyrexia (26.7%), dyspnea (25.3%), diarrhea (22%), constipation (21.7%), back pain (19.7%), cough (20%), pneumonia (19.3%), bone pain (18%), edema peripheral (17.3%), peripheral neuropathy (17.3%), muscle spasms (15.3%), and nausea (15%). Grade 3 or 4 adverse reactions (≥15% in the POMALYST + low-dose dex arm and ≥1% higher than control) included neutropenia (48.3%), thrombocytopenia (22%), and pneumonia (15.7%).

DRUG INTERACTIONS

Avoid concomitant use of POMALYST with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce POMALYST dose by 50%.

USE IN SPECIFIC POPULATIONS

Pregnancy: See Boxed WARNINGS. If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. There is a POMALYST pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALYST during pregnancy as well as female partners of male patients who are exposed to POMALYST. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.
Lactation: There is no information regarding the presence of pomalidomide in human milk, the effects of POMALYST on the breastfed child, or the effects of POMALYST on milk production. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in a breastfed child from POMALYST, advise women not to breastfeed during treatment with POMALYST.

Pediatric Use: Safety and effectiveness have not been established in pediatric patients.

Geriatric Use: No dosage adjustment is required for POMALYST based on age. Patients >65 years of age were more likely than patients ≤65 years of age to experience pneumonia.

Renal Impairment: Reduce POMALYST dose by 25% in patients with severe renal impairment requiring dialysis. Take dose of POMALYST following hemodialysis on hemodialysis days.

Hepatic Impairment: Reduce POMALYST dose by 25% in patients with mild to moderate hepatic impairment and 50% in patients with severe hepatic impairment.

Smoking Tobacco: Advise patients that smoking may reduce the efficacy of POMALYST. Cigarette smoking reduces the AUC of pomalidomide by 32% by CYP1A2 induction.

Please see full Prescribing Information, including Boxed WARNINGS.

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 gene and protein regulation. For more information, please visit the Company's website at 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. Celgene undertakes 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, 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 makes it more difficult to maintain business, contractual and operational relationships; pending legal proceedings or any future litigation instituted against Bristol-Myers Squibb, Celgene or the combined company could delay or prevent the proposed transaction; and Bristol-Myers Squibb, Celgene or the combined company is unable to retain key personnel.

References:


4 Richardson P, Rocaffigüera A, Beksaç M, et al. OPTIMISM: Phase 3 trial of pomalidomide, bortezomib, and low-dose dexamethasone vs bortezomib and low-dose dexamethasone in lenalidomide-exposed patients with relapsed or refractory multiple myeloma. Presented at: American Society of Clinical Oncology Annual Meeting; June 1, 2018; Chicago, IL.


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