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## **FDA Expands Indication for REVLIMID® (Lenalidomide) in Combination with Dexamethasone to Include Patients Newly Diagnosed with Multiple Myeloma**

*REVLIMID plus dexamethasone is now approved as an option for use in all patients with multiple myeloma*

SUMMIT, N.J.--(BUSINESS WIRE)-- Celgene Corporation (NASDAQ:CELG) today announced that the U.S. Food and Drug Administration (FDA) has expanded the existing indication for REVLIMID® (lenalidomide) in combination with dexamethasone to include patients newly diagnosed with multiple myeloma (NDMM). REVLIMID plus dexamethasone was previously approved in June 2006 for use in multiple myeloma patients who have received at least one prior therapy.

"The approval of REVLIMID as an option for use in all patients with multiple myeloma represents a new paradigm in the management of this disease," said Kenneth Anderson, M.D., Director, Jerome Lipper Multiple Myeloma Center, Dana-Farber/Brigham and Women's Cancer Center. "We now have clinical evidence demonstrating that starting and keeping newly diagnosed multiple myeloma patients on REVLIMID significantly improves progression-free survival."

The approval was based on safety and efficacy results from phase III studies, including the FIRST trial (MM-020/IFM 07-01), which evaluated continuous REVLIMID in combination with dexamethasone (Rd Continuous) until disease progression versus melphalan, prednisone and thalidomide (MPT) for 18 months as the primary analysis, and a fixed duration of 18 cycles of Rd (Rd18) as a secondary analysis, in 1,623 newly diagnosed patients who were not candidates for stem cell transplant.

In this randomized, open-label, three-arm trial, median progression-free survival (PFS), the length of time a patient lives from study randomization to disease progression or death was the primary endpoint of the study. PFS was significantly longer for patients receiving Rd Continuous (25.5 months) than for those treated with MPT (21.2 months; HR=0.72; p=0.0001). Median overall survival (OS) in the two groups was 58.9 months and 48.5 months, respectively (HR 0.75; 95% CI 0.62, 0.90) based on a March 3, 2014 interim OS analysis. Patients in the Rd Continuous arm had a 25% reduction in the risk of death compared to patients in the MPT arm.

Safety results showed that adverse reactions reported in ≥20% of NDMM patients in the Rd Continuous, Rd18 or MPT arms included diarrhea (45.5%, 38.5%, 16.5%), anemia (43.8%, 35.7%, 42.3%), neutropenia (35.0%, 33.0%, 60.6%), fatigue (32.5%, 32.8%, 28.5%), back pain (32.0%, 26.9%, 21.4%), insomnia (27.6%, 23.5%, 9.8%), asthenia (28.2%, 22.8%, 22.9%), rash (26.1%, 28.0%, 19.4%), decreased appetite (23.1%, 21.3%, 13.3%), cough (22.7%, 17.4%, 12.6%), pyrexia (21.4%, 18.9%, 14.0%), muscle spasms (20.5%, 18.9%, 11.3%) and abdominal pain (20.5%, 14.4%, 11.1%).

The most frequently reported Grade 3 or 4 events in the Rd Continuous arm (until disease progression) included neutropenia (27.8%), anemia (18.2%), thrombocytopenia (8.3%), pneumonia (11.3%), asthenia (7.7%), fatigue (7.3%), back pain (7%), hypokalemia (6.6%), rash (7.3%), cataract (5.8%), dyspnea (5.6%), DVT (5.6%) and hyperglycemia (5.3%).

"At Celgene, we are very happy with the FDA's decision, which adds information on the use of REVLIMID plus dexamethasone as a first-line treatment for multiple myeloma to the prescribing information," said Jacquelyn A. Fouse, Ph.D., President, Global Hematology and Oncology for Celgene. "Now, as part of our commitment to improving the lives of patients living with this disease, our next step is to make the benefits of this treatment regimen available to those now eligible under the expanded indication."

Celgene currently has an application under review with the European Medicines Agency (EMA) for approval to use REVLIMID for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. The EMA's Committee for Medicinal Products for Human Use (CHMP) published a positive opinion for this application in December 2014.

### **About REVLIMID®**

In the United States, REVLIMID is approved in combination with dexamethasone for the treatment of patients with multiple myeloma. REVLIMID is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy in nearly 70 countries, encompassing Europe, the Americas, the Middle East and Asia, and in combination with dexamethasone for the treatment of patients whose disease has progressed after one therapy in

Australia and New Zealand.

REVLIMID is also approved in the United States, Canada, Switzerland, Australia, New Zealand and several Latin American countries, as well as Malaysia and Israel, for 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 and in Europe for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

In addition, REVLIMID is approved in the United States 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.

### **U.S. Regulatory Information for REVLIMID<sup>®</sup>**

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

**REVLIMID<sup>®</sup> 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<sup>®</sup> 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 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<sup>®</sup> program (formerly known as the "RevAssist<sup>®</sup>" program).**

**Information about the REVLIMID REMS<sup>®</sup> program is available at [www.celgeneriskmanagement.com](http://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 hazard to the fetus

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

## WARNINGS AND PRECAUTIONS

### Embryo-Fetal Toxicity:

- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys indicates that lenalidomide produced malformations in offspring of female monkeys who received drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID. Must obtain 2 negative pregnancy tests prior to initiating therapy
- 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 28 days 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 1 month 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<sup>®</sup> Program

Because of embryo-fetal risk, REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) the **REVLIMID REMS<sup>®</sup> Program (formerly known as the "RevAssist<sup>®</sup>" Program)**. Prescribers and pharmacies must be certified with the program and patients must sign an agreement form and comply with the requirements.

Further information about the **REVLIMID REMS<sup>®</sup>** program is available at [www.celgeneriskmanagement.com](http://www.celgeneriskmanagement.com) or by telephone at 1-888-423-5436

**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 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. **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. **MDS: See Boxed WARNINGS**

**Venous and Arterial Thromboembolism:** Venous thromboembolic events (DVT and PE) and arterial thromboses are increased in patients treated with REVLIMID. A significantly increased risk of DVT (7.4%) and PE (3.7%) occurred in patients with MM after at least one prior therapy, treated with REVLIMID/dex compared to placebo/dex (3.1% and 0.9%) in clinical trials with varying use of anticoagulant therapies. In NDMM study, in which nearly all patients received antithrombotic prophylaxis, DVT (3.6%) and PE (3.8%) were reported in the Rd continuous arm. Myocardial infarction (MI, 1.7%) and stroke (CVA, 2.3%) are increased in patients with MM after at least 1 prior therapy who were treated with REVLIMID/dex therapy compared with placebo/dex (0.6%, and 0.9%) in clinical trials. In NDMM study, MI (including acute) was reported (2.3%) in the Rd Continuous arm. Frequency of serious adverse reactions of CVA was (0.8%) in the Rd Continuous arm. 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). In controlled clinical trials that did not use concomitant thromboprophylaxis, 21.5% overall thrombotic events occurred in patients with refractory and relapsed MM who were treated with REVLIMID/dex compared to 8.3% thrombosis in the placebo/dex group. Median time to first thrombosis event was 2.8 months. In NDMM study, which nearly all patients received antithrombotic prophylaxis, overall frequency of thrombotic events was 17.4% in combined Rd continuous and Rd18 arms. Median time to first thrombosis event as 4.37 months. Thromboprophylaxis is recommended and regimen is based on patients underlying risks. ESAs and estrogens may further increase the risk of thrombosis and their use should be based on a benefit-risk decision. **See Boxed WARNINGS**

**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. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08-3.41] consistent with a 92% increase in risk of death. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials

**Second Primary Malignancies:** In clinical trials in patients with MM receiving REVLIMID, an increase of invasive second primary malignancies notably AML and MDS have been observed. The increase of AML and MDS occurred predominantly in NDMM patients receiving REVLIMID in combination with oral melphalan (5.3%) or immediately following high dose intravenous melphalan and ASCT (up to 5.2%). The frequency of AML and MDS cases in the Revlimid/dex arms was observed to be 0.4%. Cases of B-cell malignancies (including Hodgkin's Lymphomas) were observed in clinical trials where patients received lenalidomide in the post-ASCT setting. Patients who received REVLIMID-containing therapy until disease progression did not show a higher incidence of invasive SPM than patients treated in the fixed duration REVLIMID-containing arms. Monitor patients for the development of second primary malignancies. Take into account both the potential benefit and risk of second primary malignancies when considering treatment with REVLIMID

**Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dex. The mechanism of drug-induced hepatotoxicity is unknown. 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

**Allergic Reactions:** Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. 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 or TEN is suspected and should not be resumed following discontinuation for these reactions. REVLIMID capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance

**Tumor Lysis Syndrome:** Fatal instances of tumor lysis syndrome (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:** Tumor flare reaction (TFR) has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash.

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 lenalidomide until TFR resolves to  $\leq$  Grade 1. In the MCL trial, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician's discretion. Patients with Grade 1 or 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR

**Impaired Stem Cell Mobilization:** A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with REVLIMID has been reported. In patients who are autologous stem cell transplant (ASCT) candidates, referral to a transplant center should occur early in treatment to optimize timing of the stem cell collection.

## ADVERSE REACTIONS

### Multiple Myeloma

- **In newly diagnosed patients** the most frequently reported Grade 3 or 4 adverse reactions in Arm Rd Continuous included neutropenia (27.8%), anemia (18.2%), thrombocytopenia (8.3%), pneumonia (11.1%), asthenia (7.7%), fatigue (7.3%), back pain (7%), hypokalemia (6.6%), rash (7.3%), cataract (5.8%), dyspnea (5.6%), DVT (5.5%), hyperglycemia (5.3%), lymphopenia and leukopenia. The frequency of infections in Arm Rd Continuous was 75%

Adverse reactions reported in  $\geq$ 20% of NDMM patients in Arm Rd Continuous: diarrhea (45.5%), anemia (43.8%), neutropenia (35%), fatigue (32.5%), back pain (32%), insomnia (27.6%), asthenia (28.2%), rash (26.1%), decreased appetite (23.1%), cough (22.7%), dyspnea (22.0%), pyrexia (21.4%), muscle spasms (20.5%), and abdominal pain (20.5%). The frequency of onset of cataracts increased over time with 0.7% during the first 6 months and up to 9.6% by the second year of treatment with Arm Rd Continuous

- **After at least one prior therapy** most adverse reactions and Grade 3/4 adverse reactions were more frequent in MM patients who received the combination of REVLIMID/dex compared to placebo/dex. Grade 3 or 4 adverse reactions included neutropenia 33.4% vs 3.4%, febrile neutropenia 2.3% vs 0%, DVT 8.2% vs 3.4% and PE 4% vs 0.9% respectively

Adverse reactions reported in ≥15% of MM patients (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%), weight decreased (20% vs 15%), nasopharyngitis (18% vs 9%), blurred vision (17% vs 11%), anorexia (16% vs 10%), and dysgeusia (15% vs 10%)

### **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%)
- Serious adverse events reported in ≥2 patients treated with REVLIMID monotherapy for MCL included chronic obstructive pulmonary disease, clostridium difficile colitis, sepsis, basal cell carcinoma, and supraventricular tachycardia
- 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, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID. It is not known whether there is an interaction between dex and warfarin. Close monitoring of PT and INR is recommended in MM patients taking concomitant warfarin. Erythropoietic agents, or other agents, that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution after making a benefit-risk assessment in patients receiving REVLIMID

### **USE IN SPECIFIC POPULATIONS**

**Pregnancy:** If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436

**Nursing Mothers:** It is not known whether REVLIMID is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother

**Pediatric Use:** Safety and effectiveness in patients below the age of 18 have not been established

**Renal Impairment:** Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CL<sub>Cr</sub> 30-60 mL/min) or severe renal impairment (CL<sub>Cr</sub> < 30 mL/min) and in patients on dialysis

**Please see accompanying full Prescribing Information, including Boxed WARNINGS.**

## About Celgene

Celgene Corporation, headquartered in Summit, New Jersey, is an integrated global biopharmaceutical 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 [www.celgene.com](http://www.celgene.com). Follow us on Twitter @Celgene, and on [Pinterest](#) and [LinkedIn](#).

## 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 Celgene Corporation's Annual Report on Form 10-K and other reports filed with the Securities and Exchange Commission.*

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Celgene Corporation

Investors:

+1-908-673-9628

[ir@celgene.com](mailto:ir@celgene.com)

or

Media:

+1-908-673-2275

[media@celgene.com](mailto:media@celgene.com)

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