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FDA Approves Merck's Single-Dose EMEND[®] (fosaprepitant dimeglumine) for Injection, in Combination with Other Antiemetic Agents, for the Prevention of Delayed Nausea and Vomiting in Adults Receiving Moderately Emetogenic Chemotherapy (MEC)

First and Only Intravenous NK₁ Receptor Antagonist Approved in the U.S. for Use in MEC

KENILWORTH, N.J., Feb. 4, 2016 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved a supplemental new drug application (sNDA) for single-dose EMEND[®] (fosaprepitant dimeglumine) for injection, Merck's substance P/neurokinin-1 (NK₁) receptor antagonist, in combination with other antiemetic medicines, for the prevention of delayed nausea and vomiting in adults receiving initial and repeat courses of moderately emetogenic chemotherapy (MEC). EMEND has not been studied for the treatment of established nausea and vomiting.

The FDA approval is supported by data from a Phase 3 study that showed single-dose EMEND for injection, combined with other anti-vomiting medicines, provided greater protection from delayed nausea and vomiting following administration of moderately emetogenic chemotherapy versus an active control regimen. With this approval, EMEND for injection is the first intravenous single-dose NK₁ receptor antagonist approved in the U.S. for both highly emetogenic chemotherapy (HEC) as well as MEC.

EMEND for injection is contraindicated in patients who are hypersensitive to any component of the product and in patients taking pimozone.

"Despite significant advances in supportive care, nausea and vomiting has remained a challenge for many cancer patients undergoing moderately emetogenic chemotherapy – and has historically required multi-day antiemetic therapy," said Stuart Green, vice president, clinical research, Merck Research Laboratories. "Today's approval of an expanded indication for EMEND for injection means that physicians now have a new single-dose intravenous option, combined with other anti-

vomiting medicines, for the prevention of delayed nausea and vomiting in these patients.”

Data Supporting the FDA Approval

The FDA approval of this new indication was based in part on findings from a randomized, parallel, double-blind, active comparator-controlled study that evaluated EMEND (fosaprepitant dimeglumine) for injection (150 mg) as a single intravenous infusion in combination with ondansetron and dexamethasone (referred to as the EMEND regimen) (n=502) compared with ondansetron and dexamethasone alone (control regimen) (n=498) in patients receiving MEC. The primary endpoint was complete response (defined as no vomiting and no use of rescue therapy) in the delayed phase (25 to 120 hours following initiation of chemotherapy) of chemotherapy-induced nausea and vomiting. A 78.9 percent complete response rate was observed with the EMEND regimen compared to 68.5 percent with the control regimen (p<0.001). The results of this trial were presented at the 2015 annual meeting of the American Society of Clinical Oncology, and have now been published in the journal *Annals of Oncology*.

The most common adverse reactions reported in the EMEND regimen versus control regimen were fatigue (15% vs 13%), diarrhea (13% vs 11%), neutropenia (8% vs 7%), asthenia (4% vs 3%), anemia (3% vs 2%), peripheral neuropathy (3% vs 2%), leukopenia (2% vs 1%), dyspepsia (2% vs 1%), urinary tract infection (2% vs 1%), and pain in extremity (2% vs 1%).

About EMEND (fosaprepitant dimeglumine) for Injection

EMEND for injection is an intravenous prodrug of the oral formulation of EMEND® (aprepitant). When EMEND for injection is administered, fosaprepitant is rapidly converted in the body to aprepitant. EMEND (aprepitant) is a selective high-affinity antagonist of human substance P/neurokinin-1 (NK₁) receptors. Aprepitant has little or no affinity for serotonin (5-HT₃), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV).

EMEND for injection, in combination with other antiemetic agents, is indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin and for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

EMEND has not been studied for the treatment of established nausea and vomiting.

Selected Important Safety Information for EMEND (fosaprepitant dimeglumine) for Injection

EMEND is contraindicated in patients who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions, flushing, erythema, and dyspnea have been reported. If symptoms occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate the infusion in patients who experience these symptoms during first-time use.

EMEND is contraindicated in patients taking pimozide. Inhibition of CYP3A4 by aprepitant, the active drug, could result in elevated plasma concentrations of this drug, which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation.

Fosaprepitant, a prodrug of aprepitant, is a weak inhibitor of CYP3A4, and aprepitant is a substrate, inhibitor, and inducer of CYP3A4. Use of EMEND with other drugs that are CYP3A4 substrates, may result in increased plasma concentrations of the concomitant drug. Use of EMEND with strong or moderate CYP3A4 inhibitors (eg, ketoconazole, diltiazem) may increase plasma concentrations of aprepitant and result in an increased risk of adverse reactions related to EMEND. Use of EMEND with strong CYP3A4 inducers (eg, rifampin) may result in a reduction in aprepitant plasma concentrations and decreased efficacy of EMEND.

Reduce the dose of the co-administered corticosteroid on Days 1 and 2 for patients receiving HEC and on Day 1 for patients receiving MEC as follows: oral dexamethasone by approximately 50%; oral methylprednisolone by approximately 50%; and intravenous methylprednisolone by approximately 25%.

Monitor patients taking vinblastine, vincristine, or ifosfamide or other chemotherapeutic agents that are metabolized by CYP3A4 for chemotherapeutic-related adverse reactions. No dosage adjustments are needed when etoposide, vinorelbine, paclitaxel, or docetaxel are administered.

Coadministration of EMEND with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in international normalized ratio (INR) of prothrombin time. In patients on chronic warfarin therapy, monitor the INR in the 2-week period, particularly at 7 to 10 days, following initiation of EMEND with each chemotherapy cycle.

The efficacy of hormonal contraceptives (including birth control pills, skin patches, implants, and certain IUDs) may be reduced during coadministration with and for 28 days after the last dose of EMEND. Advise patients to use effective alternative or backup methods of contraception during treatment with EMEND (fosaprepitant dimeglumine) and for 1 month following administration of EMEND.

In the MEC study, the most common adverse reactions reported in at least 2% of patients

treated with the EMEND regimen and at a greater incidence than the control regimen were: fatigue (15% EMEND regimen vs 13% control regimen), diarrhea (13% vs 11%), neutropenia (8% vs 7%), asthenia (4% vs 3%), anemia (3% vs 2%), peripheral neuropathy (3% vs 2%), leukopenia (2% vs 1%), dyspepsia (2% vs 1%), urinary tract infection (2% vs 1%), and pain in extremity (2% vs 1%). In the HEC study, the safety profile was generally similar to that seen in the MEC study with fosaprepitant and prior HEC studies with aprepitant.

In the MEC study, infusion-site reactions were reported in 2.2% of patients treated with the EMEND regimen compared to 0.6% of patients treated with the control regimen, including infusion-site pain (1.2% EMEND regimen vs 0.4% control regimen), injection-site irritation (0.2% vs 0.0%), vessel puncture-site pain (0.2% vs 0.0%), and infusion-site thrombophlebitis (0.6% vs 0.0%). In the HEC study, which compared fosaprepitant to aprepitant, infusion-site reactions occurred at a higher incidence in the fosaprepitant group (3.0%) than in the aprepitant group (0.5%). The following additional infusion-site reactions occurred in the HEC study and were not reported in the MEC study: infusion-site erythema (0.5% for fosaprepitant vs 0.1% for aprepitant), infusion-site pruritus (0.3% vs 0.0%), and infusion-site induration (0.2% vs 0.1%).

Our Focus on Cancer

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck Oncology, helping people fight cancer is our passion and supporting accessibility to our cancer medicines is our commitment. Our focus is on pursuing research in immuno-oncology and we are accelerating every step in the journey – from lab to clinic – to potentially bring new hope to people with cancer. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

Today's Merck is a global health care leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to health care through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on [Twitter](#), [Facebook](#), [YouTube](#) and [LinkedIn](#).

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company’s 2014 Annual Report on Form 10-K and the company’s other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

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Please see Prescribing Information for EMEND (fosaprepitant dimeglumine) for injection at http://www.merck.com/product/usa/pi_circulars/e/emend_iv/emend_iv_pi.pdf and Patient Information for EMEND (fosaprepitant dimeglumine) for injection at http://www.merck.com/product/usa/pi_circulars/e/emend_iv/emend_iv_ppi.pdf.