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Merck Announces Data from Investigational Phase 3 Study on EMEND (R) (aprepitant) for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Children Undergoing Emetogenic Chemotherapy

Merck Planning Regulatory Submissions in the U.S. for EMEND(R) in Pediatric Setting Including New Suspension Formulation in Second Half of 2014

WHITEHOUSE STATION, N.J.--(BUSINESS WIRE)--June 30, 2014--
Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced results from a global, investigational Phase 3 study to evaluate the safety and efficacy of EMEND(R) (aprepitant) in the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric cancer patients, aged 6 months to 17 years. In this study in pediatric cancer patients undergoing very highly, highly, or moderately emetogenic (vomit-inducing) chemotherapy, the use of the EMEND regimen for CINV prevention was significantly more effective than a control regimen in achieving Complete Response, defined as no vomiting or retching and no use of rescue medication for nausea and vomiting, in all phases of CINV (acute, delayed, and overall). These new data were presented in an oral session at the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) Annual International Symposium on Supportive Care in Cancer (Abstract #0286) by Dr. Hyoung Jin Kang, M.D., Ph.D., lead investigator and associate professor, Department of Pediatrics, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea.

"Nausea and vomiting are common complications of cancer chemotherapy and can be particularly distressful and debilitating to pediatric cancer patients," said Dr. Stuart Green, vice president, clinical research, Merck Research Laboratories. "In this large pediatric study, adding EMEND to a standard regimen for prevention of CINV resulted in significant reduction of emetic events."

Based on these data, Merck plans worldwide regulatory submissions for EMEND (aprepitant), beginning in the United States, for use in the prevention of CINV in pediatric and adolescent cancer patients (ages 6 months to 17 years). In the United States, Merck plans to submit a New Drug Application (NDA) for a new pediatric formulation (powder for suspension) and a supplemental NDA for use of the current formulation (capsules). Both filings are planned for the second half of 2014.

EMEND, a Substance P/Neurokinin-1 (NK1) receptor antagonist approved for use 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, including high-dose cisplatin; and for prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. EMEND has not been studied for treatment of established nausea and vomiting. Chronic continuous administration of EMEND is not recommended. Safety and efficacy of EMEND in pediatric patients have not been established.

Efficacy and Safety Findings for Investigational, Phase 3 CINV Prevention Study of EMEND in Pediatric Patients

The Phase 3 randomized, double-blind, active-comparator study of 302 participants evaluated EMEND for prevention of CINV in children (ages 6 months to 17 years of age). In the study, patients receiving emetogenic chemotherapy were randomly assigned to receive an EMEND plus ondansetron regimen (n=152) or a control regimen (placebo plus ondansetron) (n=150). The EMEND regimen included either EMEND capsules or an investigational powder for suspension formulation of aprepitant dosed based on weight. Ondansetron dosing was based on the approved pediatric dose (as per the local label). The primary endpoint of the study was complete response (no vomiting, no retching, and no use of rescue medication for nausea and vomiting) in the delayed phase (25 to 120 hours following initiation of chemotherapy). The secondary endpoints were complete response in the acute phase (0 to 24 hours) and overall phase (0-120 hours), and no vomiting in the overall phase. In both groups, the first dose of EMEND (plus ondansetron) was administered on day 1 of chemotherapy, then subsequently (without ondansetron) later on days 2 and 3. Dexamethasone could be administered intravenously per investigator discretion (the dose was based on weight). Administration of dexamethasone was similar in patients receiving the EMEND regimen and the control regimen (44 vs. 42 patients, respectively).

EMEND Regimen Increased Complete Response in Days 2 through 5 (primary endpoint)

In the study, 51 percent of patients receiving the EMEND (aprepitant) regimen achieved the primary endpoint of complete response in the delayed phase of CINV, versus 26 percent of those in the control group ($p < 0.0001$). For the secondary endpoints, 66 percent of patients receiving the EMEND regimen achieved a complete response in the acute phase of CINV, versus 52 percent of those receiving the control regimen ($p = 0.0135$). In addition, complete response in the overall phase was higher in patients receiving the EMEND regimen versus the control regimen (40% vs. 20%, $p = 0.0002$). No vomiting in the overall phase was observed in 47 percent vs. 21 percent of patients receiving the EMEND regimen compared to the control regimen, respectively ($p < 0.0001$).

Overall, 79 percent of patients receiving the EMEND regimen and 77 percent receiving the control regimen experienced one or more adverse events. The most common adverse events (across all grades) with the EMEND regimen compared to the control regimen included anemia (17% vs. 25%),

febrile neutropenia (16% for both groups), vomiting (15% for both groups), neutropenia (14% vs. 12%), thrombocytopenia (10% vs. 11%), decreased neutrophil count (9% vs. 13%), nausea (9% vs. 11%), and a decreased platelet count (8% vs. 10%). Treatment-related adverse events were observed in 3 percent (5/152) of patients receiving the EMEND regimen and in 2 percent (3/150) of patients receiving the control regimen. Serious treatment-related adverse events were observed in 1 percent (2/152) of patients on an EMEND regimen and in 0 percent (0/150) of patients receiving the control regimen.

Selected important safety information for EMEND (aprepitant)

EMEND is contraindicated in patients who are hypersensitive to any component of the product. EMEND is a dose-dependent inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

EMEND should be used with caution in patients receiving concomitant medications, including chemotherapy agents, that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by EMEND could result in elevated plasma concentrations of these concomitant medications. Conversely, when EMEND is used concomitantly with another CYP3A4 inhibitor, aprepitant plasma concentrations could be elevated. When EMEND is used concomitantly with medications that induce CYP3A4 activity, aprepitant plasma concentrations could be reduced, and this may result in decreased efficacy of aprepitant.

Chemotherapy agents that are known to be metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. In clinical studies, EMEND (aprepitant) was administered commonly with etoposide, vinorelbine, or paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. In separate pharmacokinetic studies, EMEND did not influence the pharmacokinetics of docetaxel or vinorelbine.

Because a small number of patients in clinical studies received the CYP3A4 substrates vinblastine, vincristine, or ifosfamide, particular caution and careful monitoring are advised in patients receiving these agents or other chemotherapy agents metabolized primarily by CYP3A4 that were not studied.

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, the INR should be closely monitored in the 2-week period, particularly at 7 to 10 days, following initiation of fosaprepitant with each chemotherapy cycle.

The efficacy of hormonal contraceptives (including birth control pills, skin patches, implants, and certain IUDs) may be reduced upon coadministration and for 28 days following the last dose of EMEND. Alternative or back-up methods of contraception should be used during treatment with and for 1 month following the last dose of EMEND.

Chronic continuous use of EMEND for prevention of nausea and vomiting is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

In clinical trials of EMEND in patients receiving highly emetogenic chemotherapy, the most common adverse events reported at a frequency greater than with standard therapy, and at an incidence of 1% or greater, were hiccups (4.6% EMEND (aprepitant) vs. 2.9% standard therapy), asthenia/fatigue (2.9% vs. 1.6%), increased ALT (2.8% vs. 1.5%), increased AST (1.1% vs. 0.9%), constipation (2.2% vs. 2.0%), dyspepsia (1.5% vs. 0.7%), diarrhea (1.1% vs. 0.9%), headache (2.2% vs. 1.8%), and anorexia (2.0% vs. 0.5%).

In clinical trials of EMEND in patients receiving moderately emetogenic chemotherapy, the most common adverse events reported at a frequency greater than with standard therapy were eructation (1.0% EMEND vs. 0.1% standard therapy) and fatigue (1.4% vs. 0.9%).

About CINV

Chemotherapy Induced Nausea and Vomiting (CINV) is a common side effect of chemotherapy caused by injured stomach cells that start the process of nausea and vomiting and can directly activate the area of the brain responsible for producing nausea and vomiting.

The two main types of CINV are acute and delayed. Acute happens within the first 24 hours of receiving chemotherapy. Delayed happens from day 2 to day 5 after chemotherapy. The amount and timing of CINV can vary. Some chemotherapies cause acute nausea and vomiting. Others cause acute nausea and vomiting followed by another period of delayed nausea and vomiting.

About Merck

Today's Merck is a global healthcare 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 consumer care 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 healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.

Forward-Looking Statement

This news release includes "forward-looking statements" within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck'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 healthcare legislation in the United States and internationally; global trends toward healthcare cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck'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 Merck's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck 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 Merck's 2013 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).

Please see Prescribing Information for EMEND (aprepitant) at http://www.merck.com/product/usa/pi_circulars/e/emend/emend_pi.pdf and Patient Information for EMEND (aprepitant) at http://www.merck.com/product/usa/pi_circulars/e/emend/emend_ppi.pdf

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