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**IN THE NEWS:**

“A **peer reviewer** for The New England Journal of Medicine broke confidentiality rules and leaked a negative report that indicated a potential cardiac risk for patients taking GlaxoSmithKline Plc's diabetes drug Avandia (rosiglitazone maleate), the journal Nature reported. A report published on Nature's Web site revealed the reviewer as Dr. Steven Haffner, a prominent diabetes researcher with the University of Texas Health Science Center at San Antonio. Haffner broke NEJM's nondisclosure rules by faxing a copy of the potentially damaging article to GSK's offices on May 3, more than two weeks prior to the article's publication in the journal. Haffner admitted to the leak, citing "bad judgment" and not "feeling well" rather than monetary gain as his reason for the act.

In addition to breaking the journal's rules, the leak gave GSK additional time to formulate a response to the data, Nature said. "The most troubling aspect of this situation is that the integrity of another aspect of the scientific process is called into question--scientific peer review," Sen. Charles Grassley, R-Iowa, said in a statement cited by The Wall Street Journal. Grassley has launched an investigation into the issue and sent a letter to GSK requesting information regarding how the company responded to the leak, Reuters reported. Nancy Pekarek, a spokeswoman for GSK, said the company acted appropriately and responsibly in responding to the situation insofar as it did not offer any input to Haffner regarding the information, although she was not aware of any disclosure of the breach to NEJM, Nature reported.

Just 15 days after the publication of the negative report in NEJM, GSK-funded researchers published an interim analysis of the company's RECORD trial and referenced the May report. Pekarek told Nature that the FDA had previously asked to see data from the trial, but that GSK's inside knowledge of the negative report "added an additional sense of urgency" that influenced the rapid publication of the RECORD data.”

“**Millennium Pharmaceuticals Inc.'s supplemental New Drug Application** seeking approval of Velcade (bortezomib) for the treatment of patients with newly diagnosed multiple myeloma was granted priority review designation by the Food and Drug

Administration. The sNDA included data from the Phase III VISTA study, in which 682 patients with newly diagnosed multiple myeloma who were ineligible for stem cell transplantation were randomized to receive Velcade in combination with GlaxoSmithKline Plc's Alkeran (melphalan) and prednisone or Alkeran plus prednisone alone, which is the current standard of care. Patients who received the Velcade-based regimen achieved a statistically significant improvement across all efficacy endpoints studied, including complete remission rate, time to disease progression, progression-free survival and overall survival.

During treatment, patients who received the Velcade-based regimen had an immunofixation-negative complete response rate of 35 percent compared with a rate of 5 percent among the patients who received Alkeran and prednisone alone. The immunofixation-negative complete response rate achieved by the patients in the Velcade group is the highest rate ever reported in a Phase III trial in patients with newly diagnosed multiple myeloma, according to Millennium. The company expects a potential label expansion from the FDA by June 20.

"The rapid action by the FDA puts us one step closer to establishing Velcade-based therapies as a standard of care for patients with newly diagnosed multiple myeloma," said Dr. Nancy Simonian, Millennium's chief medical officer. Velcade is approved in the United States for treating patients with multiple myeloma or mantle cell lymphoma who have received at least one previous treatment. Millennium commercializes the product in the United States; for a limited period, it is being co-promoted by Ortho Biotech Products LP in the United States. Johnson & Johnson Pharmaceutical Research & Development LLC is co-developing the product with Millennium and commercializing it in the rest of the world."

**"The Food and Drug Administration granted orphan drug** designation to GlaxoSmithKline Plc and Synta Pharmaceuticals Corp.'s elesclomol (formerly STA-4783) for the treatment of patients with metastatic melanoma. Elesclomol--which is believed to kill cancer cells by elevating oxidative stress levels beyond a breaking point, triggering programmed cell death--received fast track status in this indication in November 2006. A completed, double-blind, randomized, controlled Phase IIb trial that included 81 patients with metastatic melanoma evaluated elesclomol in combination with paclitaxel versus paclitaxel alone. Results showed that the combination group's median progression-free survival time was double that of patients in the paclitaxel-only group, meeting the trial's primary endpoint with statistical significance.

In October, the SYMMETRY trial, a pivotal Phase III trial of elesclomol in combination with paclitaxel in metastatic melanoma, was started. The companies also plan to conduct Phase II trials in other indications, and in combination with other agents. Synta and GSK are developing the drug under a global collaboration agreement."

**"The Food and Drug Administration** granted approval to Merck & Co. Inc.'s Emend (fosaprepitant dimeglumine) for injection as an intravenous therapy to prevent chemotherapy-induced nausea and vomiting. More specifically, the Emend injection is to

be used in combination with other antiemetic drugs to prevent acute and delayed nausea and vomiting that occur with courses of moderately and highly emetogenic cancer chemotherapy, including high-dose cisplatin. The approval was supported by a study that demonstrated that 115 mg of intravenous Emend was biologically equivalent to 125 mg of Merck's oral Emend (aprepitant).

Emend injection is a prodrug of the oral version of Emend, meaning that fosaprepitant in the injectable form is converted to aprepitant in the body. Patients may follow an antiemetic regimen that involves taking 115 mg of Emend injection or 125 mg of oral Emend on day 1, followed by 80 mg of oral Emend on days two and three, along with a corticosteroid and 5-hydroxytryptamine 3 receptor antagonist. Merck received an approvable letter for Emend injection in May 2007 that requested manufacturing validation and stability data. "While the oral formulation of Emend is appropriate for many patients, the approval of Emend for injection provides health care professionals and their patients with a new option in helping to prevent nausea and vomiting caused by chemotherapy," said Dr. Lee Schwartzberg, clinical oncologist and professor of medicine at the University of Tennessee Health Science Center."

**"A standard dose of Novartis AG's Gleevec (imatinib mesylate) appears effective as primary systemic therapy in patients with incurable gastrointestinal stromal tumors (GIST), although a higher dose of the drug does not appear to increase its effectiveness, according to data from a Phase III trial. Researchers conducted an open-label trial in which 746 patients with advanced GIST were randomized to receive a standard dose of Gleevec (400 mg once daily) or a higher dose (400 mg twice daily) with no blinding of drug administration. Patients were treated until disease progression or unacceptable toxicity. Results indicated overall benefits of Gleevec therapy that were consistent with previous reports. However, there were no significant differences in response between treatment groups; specifically, 5 percent of the patients who received the standard dose achieved a complete response and 40 percent achieved a partial response for an overall response rate of 45 percent, while 3 percent of the patients who received the higher dose achieved a complete response and 42 percent achieved a partial response for an overall response rate of 45 percent. Further, rates of stable disease and progressive disease were also similar between treatment groups.**

At the end of the study period, the median progression-free survival was 18 months in the standard-dose group compared with 20 months in the higher-dose group; the two-year progression-free survival rate was 41 percent in the standard-dose group compared with 46 percent in the higher-dose group. These differences were not statistically significant. Similar nonsignificant differences were observed for median overall survival and two-year overall survival estimates. "Overall, serious adverse events and deaths were more common in the high-dose [Gleevec] arm, as were dose delays and reductions," the authors of the study wrote. Compared with the standard dose, the higher dose of Gleevec "is a more toxic but not more effective dose," they concluded. The 400 mg dose "remains the standard of care when [Gleevec] is used to treat incurable GIST." These findings were published in the Feb. 1 issue of the *Journal of Clinical Oncology*."

## CLINICAL TRIALS:

**“AstraZeneca Pharmaceuticals LP's Zomig** (zolmitriptan) 2.5 mg tablets are generally as efficacious as several other triptans at treating acute migraine but are inferior to, albeit safer than, Pfizer Inc.'s Relpax (eletriptan hydrobromide) 80 mg tablets, a new investigation shows. Researchers conducted a meta-analysis of 24 randomized controlled trials that altogether involved 15,408 patients who had acute migraines. The studies made several comparisons, including weighing Zomig 2.5 mg and 5 mg tablets against the following triptans: Relpax 40 mg and 80 mg tablets, Ortho-McNeil Neurologics Inc.'s Axert (almotriptan malate) 12.5 mg tablets, GlaxoSmithKline Plc's Amerge (naratriptan hydrochloride) 2.5 mg tablets, GSK's Imitrex (sumatriptan succinate) 50 mg and 100 mg tablets and Merck & Co. Inc.'s Maxalt (rizatriptan benzoate) 10 mg tablets. Axert is licensed from Almirall SA.

The two primary efficacy outcomes were headache relief and pain freedom two hours postdose. The investigators evaluated headache relief in 20 trials that included patients with moderate to severe attacks and pain freedom and adverse events in 23 trials that involved patients with mild to severe attacks. Zomig 2.5 mg was comparable to Axert, Maxalt and Relpax 40 mg--just as Zomig 5 mg was similar to both doses of Imitrex--on the two primary efficacy outcomes. Patients were 73 percent more likely to have pain freedom at two hours if they took Zomig 2.5 mg instead of Amerge, but Relpax 80 mg was superior to Zomig 2.5 mg for both efficacy measures. However, the greater efficacy of Relpax 80 mg came with an 80 percent elevated risk for adverse events as compared with Zomig 2.5 mg.

The rate of adverse events did not significantly differ for patients who took Zomig 2.5 mg relative to those who took Axert, Relpax 40 mg and Imitrex 50 mg and for those who received Zomig 5 mg versus those who took either dose of Imitrex. The risk of adverse events increased by 59 percent and 27 percent, however, if patients were treated with Zomig 2.5 mg instead of Amerge or Maxalt, respectively. Complete study results were published in the February issue of the journal *Headache*.”

**“Patients with moderate to severe plaque psoriasis** who are treated with Centocor Inc.'s Remicade (infliximab) may achieve a consistently high level of skin clearance, according to data from an integrated analysis of three randomized, double-blind trials presented in San Antonio, Texas, at the 66th Annual Meeting of the American Academy of Dermatology. In the first trial, a Phase III study known as EXPRESS, 378 adult patients with chronic, stable plaque psoriasis involving at least 10 percent of their body surface area (BSA) were randomized to receive Remicade 5 mg/kg of body weight or placebo at weeks zero, two and six, followed by maintenance treatments every eight weeks. The patients who were initially randomized to receive placebo crossed over to Remicade therapy starting at week 24, with additional treatments administered at weeks 26 and 30 and then every eight weeks through week 46.

In the second trial, a Phase III study known as EXPRESS II, 835 adult patients who met

the same enrollment criteria used in the EXPRESS trial were randomized to receive induction doses of Remicade 3 mg/kg, Remicade 5 mg/kg or placebo at weeks zero, two and six. The patients who were initially randomized to receive either dose of Remicade were then randomized again at week 14 to receive either scheduled or as-needed maintenance therapy, which was administered at the same dose they received during the induction portion of the trial. The patients who were initially randomized to the placebo group crossed over at week 16 to receive Remicade 5 mg/kg at weeks 16, 18 and 22, and then every eight weeks through week 46.

In the third trial, a Phase II study known as SPIRIT, 249 patients with severe plaque psoriasis who had previously received psoralen plus ultraviolet light A (PUVA) or systemic therapy for psoriasis were randomized to receive Remicade 3 mg/kg or 5 mg/kg or placebo at weeks zero, two and six. The patients were assessed biweekly for 10 weeks; at 26 weeks, the patients who had Physician Global Assessment scores that indicated moderate to severe disease were eligible for an additional infusion of their assigned treatment to assess the safety of retreatment after a 20-week treatment-free period. In the combined analysis of the trials, the Remicade-treated patients achieved a consistently high level of skin clearance in the head and neck, trunk and lower and upper extremities, as measured by the Psoriasis Area Severity Index (PASI).

At week 10 of treatment, 71 percent of the patients who received Remicade 3 mg/kg and 79 percent of the patients who received Remicade 5 mg/kg achieved a 75 percent improvement in PASI criteria (PASI 75) compared with 3 percent of the patients in the placebo groups who did so. The difference in outcomes between each dosage of Remicade and placebo was statistically significant. Furthermore, 39 percent of the patients who received Remicade 3 mg/kg and 52 percent of the patients who received Remicade 5 mg/kg achieved a PASI 90 response, whereas only 1 percent of the placebo-treated patients achieved this response. "This analysis shows that treatment with Remicade resulted in a consistently high level of clinical response in each quadrant of the body evaluated by PASI, and the results were consistent with patients' overall psoriasis improvement," said Dr. Alan Menter, lead investigator. "Remicade remains an important advancement and biologic treatment option for a broad spectrum of patients with severe psoriasis."

**“Medivation Inc. expects to begin** a second Phase III trial in the second quarter to test its investigational Dimebon as a therapy for mild to moderate Alzheimer's disease. Approximately 525 patients with AD will be randomized to receive Dimebon 20 mg, Dimebon 5 mg or placebo three times daily for six months. A prior trial in Russia produced highly statistically significant results with Dimebon. The firm hopes to apply for marketing approval in 2010.”

## **POLICY:**

**“The Government Accountability Office** released a report suggesting that the Food and Drug Administration does not inspect manufacturing sites for medical devices as often as dictated by the Medical Device User Fee and Modernization Act of 2002. The

report found that the FDA fails to inspect U.S. facilities that manufacture high-risk medical devices, such as pacemakers, and medium-risk devices, such as hearing aids, every two years as required; specifically, high-risk device manufacturers were inspected only every three years and medium-risk device manufacturers were inspected only every five years. Furthermore, the GAO found that the FDA conducts few inspections of overseas facilities, and only five overseas inspections have been conducted through the FDA's Accredited Persons Inspection Program since its inception in 2004. FDA officials estimate that foreign manufacturers of high-risk devices were inspected every six years, while medium-risk device manufacturers were inspected every 27 years.”

**GENERIC:**

“**Wyeth and its partner Nycomed launched a generic** version of Wyeth's blockbuster heartburn drug Protonix (pantoprazole sodium) tablets, in response to the at-risk launch of generic pantoprazole tablets in the United States by Teva Pharmaceuticals USA Inc. on Dec. 21, 2007. After Teva's launch, Teva and Wyeth had agreed to a standstill period during which they could work toward a settlement, according to Teva; Teva stopped selling its version of the drug, but noted this latest launch voided the standstill agreement. Wyeth and Nycomed previously sought a preliminary injunction against the sales of Teva's generic version, claiming patent protection until 2010, but that motion was denied. Wyeth appealed the decision and a trial is expected in the second half of this year. Prasco Laboratories will distribute Wyeth's generic version of the drug, beginning immediately. Several companies announced they will begin selling their generic versions immediately also.”

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