ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Nilotinib Risk Evaluation and Mitigation Strategy

Maria Baer, MD
Professor of Medicine
University of Maryland School of Medicine
Director, Hematologic Malignancies
University of Maryland Greenebaum Cancer Center
Baltimore, Maryland

H&O Why does the US Food and Drug Administration (FDA) require a Risk Evaluation and Mitigation Strategy (REMS), and what is it?

MB The FDA Amendments Act of 2007 gave the FDA the authority to require an REMS from drug manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. An REMS is required for some drugs or biological products in order to provide education to patients and physicians on how to monitor and minimize risk.

H&O Why was an REMS needed for nilotinib?

MB Nilotinib (Tasigna, Novartis) is a very beneficial drug that adds to the treatment armamentarium for chronic myelogenous leukemia (CML). It was FDA approved in October 2007 for adult chronic- and accelerated-phase CML resistant to, or intolerant of, imatinib (Gleevec, Novartis), and FDA approved in June 2010 for first-line therapy based on a comparative study with imatinib. However, like some other drugs, nilotinib can cause QTc prolongation, which is an electrocardiogram (ECG) abnormality that can be associated with sudden death. Because it is important to minimize the risk of QTc prolongation and to monitor for it, the FDA required that the manufacturer of nilotinib create an REMS to make patients and physicians aware of this risk (Table 1). The goals of the nilotinib REMS are to minimize the occurrence of QTc prolongation and its potential adverse consequences, to reduce medication errors involving drug-food interactions and incorrect dosing intervals, to minimize potential drug-drug interactions, and to inform healthcare providers and patients about the serious risks associated with nilotinib treatment, including QTc prolongation.

H&O What are the components of the nilotinib REMS?

MB The nilotinib REMS includes a medication guide and a communication plan (Table 2). The medication guide is dispensed with each prescription of nilotinib in order to provide information on possible QTc prolongation. The medication guide states that the QTc interval has to be monitored by an ECG before starting drug, 7 days after starting drug, and any time the dose is changed. Patients who have a baseline QTc prolongation as an abnormality should not receive nilotinib. Electrolyte abnormalities such as low potassium and magnesium can result in or exacerbate prolonged QTc interval; therefore, potassium and magnesium levels should be checked and corrected in order to minimize that risk. Food intake may also contribute to QTc prolongation. Taking nilotinib in conjunction with food increases nilotinib blood levels, thereby increasing the risk of QTc prolongation. Because of this, nilotinib must be taken on an empty stomach. Patients are told not to eat for 2 hours before and 1 hour after taking nilotinib. Specific foods can also increase

Table 1. Goals of the REMS

The goals of the REMS are to:
• Minimize the occurrence of QT prolongation and its potential cardiac sequelae.
• Reduce medication errors involving drug-food interactions and incorrect dosing intervals.
• Minimize potential interactions (drug-drug and disease-drug).
• Inform patients about the serious risks associated with Tasigna treatment.
• Inform healthcare providers about the serious risks associated with the use of Tasigna, including QT prolongation.

Note: Table adapted from the nilotinib REMS found on FDA.gov.

Table 2. Components of the Nilotinib REMS

Medication Guide Novartis will ensure that a Medication Guide is dispensed with each prescription of Tasigna and in accordance with 21CFR 208.24. The Medication Guide is part of the REMS.
Communication Plan Novartis will conduct the following: *Communication Plan* • Within 3 months of approval of the REMS and quarterly thereafter, Novartis will hand deliver and discuss educational materials with likely Tasigna prescribers; that is, the approximately 6,000 US prescribers who treat patients for chronic myelogenous leukemia (CML). • Where access to the likely prescriber is not available for hand delivery of the materials, the materials will be delivered to the likely prescriber by shipment. • In cases of shipment of materials, Novartis will attempt to make direct follow-up contact with the prescriber to discuss the REMS materials. • Each kit of educational materials will consist of the following elements: – Dear Healthcare Professional "REMS Introductory Letter" – Tasigna Educational Materials: ♦ Tasigna (nilotinib) Safety and Administration Brochure ♦ Patient Education Resource Kit Tasigna (nilotinib) – Medication Guide – Tasigna (nilotinib) Important Information about Tasigna Brochure – Drug Timing Dial – Medication Wallet Card
Timetable for Submission of Assessments REMS assessments will be submitted to the FDA at 18 months, 3 years, and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Novartis will submit each assessment so that it will be received by the FDA on or before the due date.

Note: Table adapted from the nilotinib REMS found on FDA.gov.

the risk of QTc prolongation, notably grapefruit and grapefruit juice, and these should be avoided while taking nilotinib. In addition, nilotinib is taken twice a day, so it is important to take it every 12 hours and not at closer intervals, which may result in higher blood levels. Patients are advised that if they miss a dose, they should not take an extra dose to compensate. Medication interactions can also increase the risk of QTc prolongation. Patients should take only medications prescribed or approved by their physicians while taking nilotinib, and physicians should be aware of the relevant medication interactions. These include other medications that can prolong the QTc interval (such as various antiarrhythmics, antibiotics, antidepressants, and antipsychotic medications), and medications that are CYP3A inhibitors (such as azole antifungal agents, HIV protease inhibitors, and macrolide antibiotics) or inducing agents (such as anticonvulsants and rifampicin).

H&O What is some of the important information the community should know about nilotinib?

MB QTc prolongation is the most important and most serious risk associated with nilotinib. There are some other risks, such as decreased blood counts, so it is important to monitor blood work. Rarely, nilotinib can cause pancreatitis, and that needs to be monitored as well. Individuals who have a history of pancreatitis may be more prone to developing it again, including while taking nilotinib. Patients who develop abdominal pain or vomiting need to be evaluated for possible pancreatitis. Uncommonly, nilotinib can cause liver toxicity, and patients should be properly monitored with blood work at intervals. Further, it is also important to monitor for efficacy of nilotinib, or response of the leukemia, by observing not only blood counts, but also the decrease in the percentage of cells with the t(9;22) translocation, or Philadelphia chromosome, in the bone marrow by cytogenetic analysis and the decrease in the amount of BCR-ABL transcript, encoded by the t(9;22) translocation region, by reverse transcription polymerase chain reaction molecular analysis.

H&O What is the responsibility of patients and pharmacies that are enrolled in the nilotinib REMS?

MB It is mandated that when patients receive nilotinib at the pharmacy, they receive a medication guide with all of the appropriate information along with a device (Drug Timing Dial) that reminds them to take the medication every 12 hours and not more frequently. A physician does not have to register to participate in the REMS, so it is not a very cumbersome process. The responsibility of the physician, aside from writing the prescription, is to tell the patient verbally about the contraindications and possible side effects associated with the drug.

H&O What kind of impact does the REMS have on nilotinib use?

MB This REMS has a very positive impact on nilotinib in terms of informing physicians and patients about possible risks, problems to watch for, and the proper way to take the medication. There is really no downside to the REMS.