



### TABLE OF CONTENTS

• Risk Evaluation and Mitigation Strategy (REMS)	1-2
• New ACCP Thrombosis Guidelines	2-3
• New Cancer Data with Vytorin	3-4
• P&T Committee Formulary Action	4

### Risk Evaluation and Mitigation Strategy (REMS)

Although the United States Food and Drug Administration (FDA) was established in the mid-1800s, it was not until the thalidomide tragedy of the 1960s that a rigorous drug approval process was established through the Kefauver Harris Amendment in 1962. Despite the comprehensive process mandating safety and efficacy of drugs prior to approval, the FDA has been scrutinized over the past decade for what some believe to be a drug safety crisis. This belief stems from high profile incidences such as rofecoxib (Vioxx) and its withdrawal from the market in 2004 due to post-marketing studies that demonstrated an increase in cardiovascular events. Rofecoxib was associated with nearly 28,000 deaths and is arguably the most notable pitfall that drove the FDA and Congress to call for drug safety reform. Other noteworthy incidences include rosiglitazone (Avandia) and its post-marketing studies revealing an increased risk of myocardial ischemic events and antidepressants increasing the risk of suicidal ideation.

In response to the need for reform, the Food and Drug Amendments Act (FDAAA) was signed into law on September 27, 2007. The amendment reauthorized and modified several drug provisions. Furthermore, the Risk Evaluation and Mitigation Strategy (REMS) evolved from this amendment and is a safety program that will serve as the new framework for risk management (Table 1). As of March 25, 2008, all sponsors of drug and biological products which the FDA believes have safety concerns will be required to participate in this program.

Elements for safe use of drugs are defined by the FDAAA as any of the following:

- Health care providers who prescribe the drug have particular training or experience, or are specially certified.

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified.
- The drug is dispensed to patients only in certain health care settings, such as hospitals.
- The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results.
- Each patient using the drug is subject to certain monitoring.
- Each patient using the drug is enrolled in a registry.

**Table 1. Products deemed to have an approved REMS**

Generic Name	Brand Name
Alosetron	Lotronex
Alvimopan	Entereg
Ambrisentan	Letairis
Bosentan	Tracleer
Clozapine	Clozaril, Fazaclo ODT
Dofetilide	Tikosyn
Eculizumab	Soliris
Fentanyl PCA	Ionsys
Fentanyl citrate	Actiq
Isotretinoin	Accutane, Amnesteem, Claravis, Sotret
Lenalidomide	Revlimid
Mifepristone	Mifeprex
Natalizumab	Tysabri
Romiplostim	Nplate
Small pox (Vaccinia) Vaccine, Live	ACAM2000
Sodium oxybate	Xyrem
Thalidomide	Thalomid

Although the FDA had authority in the past to regulate which drugs are allowed on or taken off the market, their power to manage them during post-approval has been limited. The enactment of the FDAAA, however, has expanded the FDA's authority. The agency is now allowed to regulate the safe use of drugs or biological products

during both clinical development and post-approval phases through REMS. A REMS is to include a comprehensive method to minimize post-marketing risks and can include, but is not limited to the following:

- Medication guide
- Patient package insert
- Communication plan
- Elements to assure safe use
- Implementation system.

This type of drug safety regulation is particularly relevant for products with known or potentially harmful risks that require close monitoring for safe use. For example, clozapine (Clozaril) can be an effective treatment for schizophrenia, but due to the risk for agranulocytosis, the drug is generally reserved for patients who fail other antipsychotic therapy. By restricting distribution of certain drugs and biological products through structured safety programs, the hope is to improve their use and effectiveness while minimizing known or potential drug risks as much as possible.

Risk Minimization Action Plan (RiskMAP) is a similar safety method that will likely be phased out with the introduction of REMS. This voluntary program has been available for the management of beneficial but potentially harmful products since 2005. One of the primary differences between the 2 drug safety methods is that with increased authority through the FDAAA, REMS allows the FDA to manage drugs during post-marketing and is mandatory upon FDA request. Currently, all products with a RiskMAP are required to submit a REMS.

Any new drug or biological product seeking approval for market by the FDA must also submit a REMS with the New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or Biologics License Application (BLA) if the FDA deems appropriate during its clinical development. The FDA has also reviewed and identified products requiring REMS but approved prior to March 25, 2008.

Healthcare professionals should be aware of those drugs with a REMS and use caution with their administration. Restrictions and procedures to obtain these drugs will vary depending on the product. Once the FDA reviews and approves the REMS, guidelines will likely be located on the FDA website at [www.fda.gov](http://www.fda.gov) and through the respective manufacturer's website. Although the time frame for REMS review and approval by the FDA appears somewhat unclear at this time, healthcare providers should be prepared for any changes to come.

### **Conclusion**

With increased authority of the FDA on the safe use of beneficial but potentially harmful drugs, including more post-marketing power, the first notice to applicable drug and biological product sponsors has been announced. The expectation with the development of REMS and the ongoing effort for drug safety is that closer monitoring will

be conducted for potentially dangerous products. This will further ensure that the benefits associated with a product's use outweigh the risks as more evidence becomes available during post-approval. Healthcare professionals should take extra caution when handling such products and be able to locate and adhere to the drug's REMS procedure when necessary.

### **New ACCP Thrombosis Guidelines**

The 8th edition of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines was published as a supplement to the June 2008 issue of Chest. The new ACCP recommendations contain much more information than the previous edition, which was published in 2004. The executive summary of the guidelines provides a good overview of recommendations discussed throughout the document. Expanded information on vitamin K antagonists, parenteral anticoagulants, and preventing and treating thrombosis during the perioperative period and in pregnant women and children are summarized in this section of the RxPress.

#### ***Vitamin K antagonists***

In 2007, the prescribing information for warfarin was updated to include information on using pharmacogenetic testing to optimize initial drug dosing. The ACCP recommends against using pharmacogenetic-based initial dosing of warfarin until additional randomized data indicate that it is beneficial. The guidelines state that warfarin should be initiated at 5 or 10 mg for the first 1 or 2 days for most patients, with subsequent dosing based on the international normalized ratio (INR) response. Patients who are elderly or malnourished; have congestive heart failure, liver disease, or recent major surgery; or are taking medications known to increase sensitivity to warfarin should be started at doses of 5 mg or less with subsequent dosing based on INR response.

#### ***Parenteral anticoagulants***

Many clinicians have wondered how to effectively monitor the use of low-molecular weight heparins (LMWHs). The ACCP has taken a strong stance against the routine monitoring of anti-Xa levels in patients treated with LMWHs. However, the guidelines recommend that routine monitoring of anti-Xa levels be performed in pregnant women treated with therapeutic doses of LMWH. Other recommendations include using weight-based dosing of LMWHs for obese patients, using unfractionated heparin (UFH) instead of LMWHs in patients with a creatinine clearance (CrCl) of less than 30 mL/min, and adjusting the dose of LMWHs appropriately if used in patients with renal insufficiency (CrCl <30 mL/min).

### **Preventing venous thromboembolism**

The ACCP recommends that all hospitals develop an institution-wide policy addressing prevention of venous thromboembolism. Routine thromboprophylaxis should be recommended for most hospitalized patient groups because almost all hospitalized patients have one or more risk factor for venous thromboembolism. ACCP specifically recommends that the policy be in written form and that strategies such as computer decision support systems, preprinted orders, and periodic audit and feedback be used to increase thromboprophylaxis adherence.

Aspirin should not be used as monotherapy in any patient group for preventing venous thromboembolism because it is not effective. Mechanical methods of thromboprophylaxis, such as graduated compression stockings, intermittent pneumatic compression devices, and the venous foot pump, are recommended for patients at high risk of bleeding or as an adjunct to anticoagulation-based thromboprophylaxis. The ACCP gives extensive recommendations on using thromboprophylaxis therapy in patients undergoing various types of surgical procedures and for acutely ill medical patients.

### **Perioperative management**

For the first time, the guidelines have an entire section discussing the management of patients on antithrombotic therapy who require surgery. The document discusses the following options:

- Stopping warfarin therapy altogether around 5 days before surgery and instead using subcutaneous LMWH or intravenous (IV) UFH for coverage of high-risk patients. For cost containment, LMWH should be administered on an outpatient basis, with the last dose given 24 hours before surgery.
- Stopping antiplatelet therapies such as aspirin- or clopidogrel-containing drugs 7 to 10 days before a procedure.
- Continuing warfarin or aspirin therapy in patients undergoing minor dental or dermatologic procedures, or cataract removal.
- Treating patients who are receiving warfarin and who require reversal of the anticoagulant effect for an urgent procedure with low-dose (2.5–5.0 mg) IV or oral vitamin K.

### **Special populations**

The guidelines have added extensive information on preventing and managing thrombosis in pregnant women and children. The following are key recommendations for pregnant women:

- Women receiving anticoagulation for managing venous thromboembolism (such as warfarin) who become pregnant should be switched to UFH or LMWH (if appropriate).
- Women with mechanical valves who become pregnant should be given either adjusted-dose twice-daily LMWH or UFH throughout pregnancy or adjusted-dose twice-daily LMWH or UFH until

the 13th week, with substitution by warfarin until LMWH or UFH are resumed close to delivery.

- For women on long-term warfarin who are attempting pregnancy and are candidates for UFH or LMWH, frequent pregnancy tests are recommended with substitution of warfarin once pregnancy is achieved.
- Alternatively, warfarin can be substituted with UFH or LMWH before conception.

Expanded recommendations for children address preventing and managing thrombosis related to congenital heart disease interventions, including ventricular assist devices and prosthetic heart valves. Children with arterial ischemic stroke should receive initial antithrombotic therapy until underlying causes are determined, followed by maintenance therapy to prevent long-term recurrence.

### **New Cancer Data with Vytorin (ezetimibe/simvastatin)**

#### **SEAS Results Alarming**

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial randomized 1873 patients to ezetimibe/simvastatin (Vytorin) 10 mg/40 mg or placebo for a mean of 4.1 years. The trial results were alarming because a statistically significantly increased incidence in new onset of cancer was observed in patients randomized to ezetimibe/simvastatin (101 patients) compared with placebo (65 patients, uncorrected  $p=0.006$ ). The cancers were not clustered in any one particular area, with increases seen in prostate, skin, gastrointestinal, and other types of cancers.

#### **SHARP and IMPROVE-IT Analyzed**

These results prompted Richard Peto, Oxford University, and colleagues to compare the incidence of cancer from the SEAS trial with the combined incidence observed in 2 currently ongoing trials: the Study of Heart and Renal Protection (SHARP) trial and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). The analysis was published on-line on September 2nd in the *New England Journal of Medicine*. In the SHARP trial, 9264 patients were randomized to ezetimibe/simvastatin 10 mg/20 mg or placebo and followed for a mean of 2.7 years, and in IMPROVE-IT, 11,353 patients were randomized to ezetimibe/simvastatin 10 mg/40 mg or simvastatin 40 mg and followed for a mean of 1 year.

Combined results from the SHARP and IMPROVE-IT studies did not find an increased incidence of cancer in patients randomized to ezetimibe/simvastatin (313 cases) compared to those not given the drug (326 cases,  $p=0.61$ ). In addition, no specific trend towards one type of cancer was noted in the SHARP and IMPROVE-IT studies, and a non-significant increase in cancer deaths in the ezetimibe/simvastatin group was observed in these 2 trials (97 deaths versus 72 in the control group,  $p=0.07$ ). The investigators did note; however, that the number of cancer deaths became significant in the ezetimibe/simvastatin group when data from all 3 trials were

combined (134 deaths versus 92 in the control group, uncorrected  $p=0.007$ ). They attributed this finding to chance, stating that an increased risk of cancer death with ezetimibe/simvastatin should have been matched with an increase in the risk of cancer, which was not observed in their analysis. The investigators concluded that there is no credible evidence to link ezetimibe/simvastatin to cancer.

In an accompanying editorial also published on-line in the same journal, Jeffery Drazen and colleagues cautioned clinicians that the current finding of increased cancer deaths may not be due to chance. They stated that ezetimibe inhibits the absorption of "molecular entities that could conceivably affect the growth of cancer cells." They also pointed to the fact that the combined analysis of all 3 trials resulted in increased cancer-related mortality. The editorial concluded that further data with longer follow-up times are needed before sound safety conclusions about ezetimibe/simvastatin can be drawn.

### ***FDA Investigating***

The Food and Drug Administration (FDA) is currently conducting its own safety analysis on the risk of cancer with ezetimibe/simvastatin, with findings to be released sometime in 2009. The FDA noted that most large prospective studies of statin drugs have reported no difference in cancer incidence between active therapy and placebo. For example, the incidence rate for cancer in the Heart Protection Study ( $n=20,000$ ) was 7.9% in patients randomized to simvastatin 40 mg/day compared with 7.8% in patients given placebo. The FDA recommends that patients talk to their healthcare provider if they have questions surrounding the safety of ezetimibe/simvastatin. Patients are advised NOT to stop their lipid-lowering therapy before discussing any changes with their prescriber. Until additional data become available, clinicians should follow the current recommendation of treating patients with maximally tolerated doses of statins alone as first-line therapy to lower low-density lipoprotein (LDL) cholesterol.

## **P&T Committee Formulary Action**

### **Deletions**

- Triamcinolone hexacetonide injection

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