

# PEDIATRIC PHARMACOTHERAPY

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## Pediatric Medications and the Development of REMS

*David M. Crowther, Pharm.D.*

Mitigating drug-associated patient risk is a significant concern not only for healthcare providers but also the Food and Drug Administration (FDA). This is apparent not only by the increasing numbers of strategic drug safety programs but also by their ever increasing complexity. As the area of risk mitigation continues to grow, it is important to understand how healthcare has arrived at its current state.

### History of Risk Management and the FDA

Over time, risk management has become continually more involved and complex. One of the earliest tools used by the FDA to manage medication-associated risks was product labeling, particularly the use of boxed warnings. These warnings, more commonly referred to as black box warnings, are the strongest cautions issued by the FDA. Another early tool was the use of "Dear Prescriber" or "Dear Doctor" letters, wherein manufacturers could communicate crucial information directly to prescribers. During the 1970s, the use of Patient Package Inserts quickly expanded with the widespread use of oral contraceptives.<sup>1</sup>

During the 1990s, Medication Guides began to be used for relaying safety information to patients. During this time, more medications began to be "fast tracked" through the FDA approval process in order to meet demands for treating specific conditions. In the late 1990s and early 2000s, there was an emergence of serious safety concerns associated with many of these "fast tracked" medications resulting in drug withdrawal from the U.S. market. In 2005, the FDA implemented Risk Minimization Action Plans (RiskMAPs). RiskMAPs were the first strategic drug safety programs developed in an effort to address rising safety concerns. These drug safety programs were developed for medications requiring risk management beyond a simple description of risks versus benefits or routine safety reporting.<sup>1,2</sup> With the passage of the Food and Drug Amendment Act of 2007, the

FDA's postmarketing authority was enhanced. The FDA could now require manufacturers to conduct postmarketing studies and submit, implement, and assess Risk Evaluation and Mitigation Strategies (REMS), replacing the previous strategic drug safety programs, RiskMAPs.<sup>2</sup>

### REMS: Purpose and Components

The purpose of REMS programs is to assure that potential benefits outweigh potential risks of drug use. The utilization of REMS programs has grown significantly. In 2007, just prior to the initiation of REMS, there were 30 medications with RiskMAPs in place. Currently, there are over 160 medications with strategic drug safety programs meeting REMS criteria.<sup>3</sup> There are 3 possible components from which each program can be built, tailored to the level of risk and the most effective method to mitigate that risk. Potential REMS components include:

- Medication Guide
- Communication Plan
- Elements to Assure Safe Use (ETASU)

Medication Guides are handouts accompanying prescription medications which address issues related to a specific drug or drug class. The information contained in the Medication Guide must be approved by the FDA and is intended to help patients avoid serious adverse events or improve drug efficacy. Distribution of medication guides is required when the use of patient labeling may prevent serious adverse effects; associated risks are serious enough that patients should be made aware prior to initiating therapy; or patient adherence is critical to drug efficacy.<sup>2</sup>

Communication plans are simply methods of disseminating information to healthcare providers regarding drug-related risks and correlating REMS programs. These communication plans can involve the standard "Dear Prescriber" letters, formal communication

to healthcare administrators, notification to professional societies, advertising of REMS programs in medical journals, or any other creative and effective methods of disseminating the information.<sup>2</sup>

Elements to Assure Safe Use (ETASU) are typically the classic examples healthcare providers associate with REMS programs. They are intended to provide safe access to drugs with known serious risks. Implementation of ETASU is only required for drugs:

- Associated with such serious adverse events that they can be approved only if, or would be withdrawn unless, ETASU were required
- Initially approved without ETASU but other REMS elements are not sufficient to mitigate such serious risk

Examples of ETASU include: formal training for those prescribing or dispensing the drug; regular and documented monitoring; enrollment in a registry; or dispensing restricted by healthcare setting, by documentation of sufficient health, or by specialty pharmacy.<sup>2</sup>

#### How Do the Pieces Fit?

The term REMS is the overarching category for FDA-governed risk management components. Products that would previously have been approved with a RiskMAP or Medication Guide are now approved with a REMS program. Existing risk management plans requiring ETASU will now be considered as having a REMS program, while other risk management plans in place prior to September 27, 2007 will continue as they have.<sup>2</sup>

#### Assessment and Enforceability

Following the approval of a REMS program by the FDA, periodic assessment is required. All programs must be formally assessed at 18 months, 3 years, and 7 years post-REMS approval. This creates significantly more work for manufacturers during the postmarketing phase. The FDA holds manufacturers responsible for complying with the approved REMS programs. Any situations of noncompliance can result in the drug being considered misbranded with up to \$250,000 per incident.<sup>2</sup>

#### Pediatric Medications Involving REMS

As pediatric patients are at higher risk for adverse drug events than adults, many of the REMS programs associated with medications used in pediatric patients are more complex. Examples of specific REMS programs will be discussed in order of increasing complexity.

#### **Levetiracetam (Keppra® or generic)**

Due to concerns of suicidal ideation associated with its use, levetiracetam was included in a meta-analysis performed by the FDA. This meta-analysis analyzed placebo-controlled trials involving 11 antiepileptic drugs (AEDs). The studies included more than 2,400 pediatric patients (< 18 years of age). Results demonstrated a statistically significant difference in the incidence of suicidal thoughts/ideation between patients receiving AEDs compared to placebo (OR 1.8; 95% CI, 1.24 to 2.66).<sup>4</sup>

In response to these findings, a REMS program was implemented for levetiracetam and the other 10 AEDs. The levetiracetam REMS program requires distribution of an approved medication guide with each dispensing of the drug. There is no required communication plan or implementation of ETASU.<sup>3,5</sup>

#### **Etanercept (Enbrel®)**

An 8 year old Caucasian female, previously diagnosed with systematic juvenile idiopathic arthritis and treated with etanercept, presented with 24 hours of fever, profuse vomiting, diarrhea, total body rash, and mild confusion. Blood cultures were positive for Group A *Streptococcus*, and the patient's purpuric rash rapidly progressed to necrosis of the extremities. It was determined to be Group A *Streptococcus* purpura fulminans. Following multiple limb amputations, the patient eventually died. The patient's etanercept therapy was identified as a significant contributing factor to this severe pyrogenic infection.<sup>6</sup>

Throughout the late 1990s and early 2000s, case reports similar to this, involving serious infection, began to be reported more frequently in patients receiving anti-tumor necrosis factor (TNF) alpha therapy. Though most of the data were from adults, there have been several documented cases involving pediatric patients.<sup>6</sup>

As a result, a REMS program was established to inform patients about the risks of serious infection and cancer associated with the drug. It is also to inform prescribers about unrecognized histoplasmosis and other invasive fungal infections associated with the drug class. The REMS program requires distribution of a medication guide as well as a communication plan involving "Dear Prescriber" letters and an educational slide presentation for prescribers, all of which are accessible from the etanercept internet site. No ETASU are required by this REMS program.<sup>3,5</sup>

### **Alglucosidase alpha (Lumizyme®)**

Alglucosidase alpha is approved as enzyme replacement therapy for patients with late onset, noninfantile Pompe disease, a genetic alpha-glucosidase deficiency. Severe immunologic reactions including anaphylaxis are risks associated with the administration of any recombinant human proteins, and alglucosidase alpha is no exception. Last year, van der Ploeg and colleagues confirmed the data presented in the alglucosidase alpha product labeling regarding the increased risk of anaphylaxis and other severe allergic reactions associated with drug administration. Of the 60 patients receiving alglucosidase alpha, 5% experienced anaphylactic reactions. With such rates of serious reactions, the FDA mandated that the manufacturer implement methods for mitigating that risk. The resultant REMS program is very involved.<sup>7</sup>

The alglucosidase alpha REMS program requires the risks of rapid disease progression and severe immune mediated reactions be communicated to both patients and prescribers. The program does not require distribution of a medication guide or documented monitoring parameters. The required elements include: a communication plan; enrollment of the patient, prescriber, and healthcare facility into the Lumizyme ACE (Alglucosidase Alfa Control and Education) Program; training of prescribers and pharmacy personnel prior to enrollment and maintenance of that certification; and distribution restrictions by healthcare facility.<sup>3,5</sup>

### **Isotretinoin (Accutane®, Amnesteem®, Claravis®, Sotret®, or generic)**

The teratogenic effects of retinoids were first documented in humans during the early 1980s. It is well established in the literature that their use during pregnancy can result in anomalies of the ears and auditory canals, facial and palatal defects, neurologic damage, heart defects, and spontaneous abortion.<sup>8</sup>

There have been multiple strategic drug safety programs implemented since the approval of isotretinoin. The most recent, iPledge, was implemented as a RiskMAP but it also meets the requirements for a REMS program. The iPledge program addresses the risk of fetal harm and teratogenicity associated with pregnancy while the drug remains at specified serum concentrations. This is one of the more involved of the current REMS programs requiring: distribution of a medication guide; enrollment of the patient, prescriber, pharmacy, and pharmacy

distributor into iPledge; monthly pregnancy testing, if applicable; and documentation of 2 chosen forms of birth control, if applicable.<sup>3,5,9</sup>

### **Sacrosidase (Sucraid®)**

Sacrosidase is oral replacement therapy for patients with genetic sucrase deficiency. In 2008, sacrosidase was reformulated and there was concern regarding potential allergic reactions to the new formulation for patients with sensitivities to yeast, yeast products, or glycerin. Though no such reactions had been documented, a REMS program was established due to the potential risk.

This was an involved REMS program consisting of communication plans, enrollment of both the patient and the prescriber into a special prescribing program, and restricted drug distribution. In December 2010, following the 18 month assessment of the sacrosidase REMS program, the FDA determined that REMS was no longer needed to assure that the benefits of sacrosidase outweighed the associated risks. The REMS program was subsequently ended.<sup>3,5</sup>

### REMS Resources

The Food and Drug Association website, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>, provides a table layout of drugs with current REMS programs, dates of approval or last revision, the associated REMS components, and links to all REMS documents filed with the FDA. This resource is helpful to identify the REMS components involved, but it only lists drugs with formally designated REMS programs. Drugs requiring medication guides or RiskMAPs prior to the institution of REMS may not be contained in this resource. For a comprehensive list of drugs requiring a medication guide, the user must search a different resource on the FDA website.<sup>3</sup>

The American Society of Health-System Pharmacists website, [www.ashp.org/REMS](http://www.ashp.org/REMS), houses a REMS Resource Center which is organized by generic drug name. For each drug, the Resource Center provides an outline of: why REMS is required; whether enrollment in a program is required and who must enroll; and which REMS components are involved. One significant advantage is that this resource is comprehensive for all formal risk management strategies. Whether the user is trying to identify drugs with a formal REMS program or pre-2007 drugs only requiring a medication guide, all products involving a risk management strategy are identified in this single resource.<sup>5</sup>

## Summary

The number of REMS programs is increasing. It is important to understand what REMS are and how they operate, especially with their varying levels of complexity. One of the most critical items for healthcare providers to know is where to find comprehensive reputable information regarding REMS programs. Through awareness and increased experience with REMS programs, the healthcare community can assure compliance and decrease risks to the patient.

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## **Pharmacology Literature Update**

### Comparing Registries and Databases

The relative effectiveness of adverse drug event reporting systems has been a long-standing debate in the medication safety literature. The authors of this study compared the ability of two systems, the United Kingdom (UK) General

Practice Research Database (GPRD), one of the world's largest databases of longitudinal primary care records, and the UK Epilepsy and Pregnancy Register, a voluntary observational system, to identify the risk for malformations with first-trimester antiepileptic (AED) exposure. Although the GRPD contained fewer cases, both systems identified an increased risk in women taking AEDs, compared to those with no AED exposure. Statistical significance was achieved only when using the Epilepsy and Pregnancy Register. The authors discuss the benefits of each system and suggest use of databases such as the GPRD for older, off-patent drugs when registries are not available.

### **Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/28/11:

1. Tocilizumab (Actemra<sup>®</sup>) was added to the Formulary, with restriction to Rheumatology and to patients with an inadequate response to anti-TNF agents.
2. Dabigatran etexilate (Pradaxa<sup>®</sup>) was added to the Formulary for use in patients with non-valvular atrial fibrillation. Dabigatran is the first oral direct thrombin inhibitor.
3. Tranexamic acid (Cyklokapron<sup>®</sup>), an antifibrinolytic, was added to the Formulary with restriction to use in total knee or total hip arthroplasty.
4. Laronidase (Aldurazyme<sup>®</sup>) was also added to the Formulary. Laronidase is a human enzyme replacement indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I and patients with the Scheie form who have moderate to severe symptoms.
5. The restrictions on the prescribing of fosphenytoin have been removed.

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