REMS: Application for the Advanced Practitioner in Oncology

WENDY H. VOGEL, MSN, FNP, AOCNP®, and MARILYN HAAS, PhD, ANP-C

From Kingsport Hematology Oncology Associates, Kingsport, Tennessee, and CarePartners, Asheville, North Carolina

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Correspondence to: Wendy Vogel, MSN, FNP, AOCNP®, 405 Pettyjohn Rd, Kingsport, TN 37664. E-mail: wvogel@charter.net

Abstract

Title IX of the 2007 Food and Drug Administration Amendments Act (FDAAA) authorizes the FDA to require pharmaceutical and biological sponsors to develop and manage a Risk Evaluation and Mitigation Strategy (REMS) program for products with certain safety issues to ensure that the benefits of the drug or biological product outweigh its risks. The ability to prescribe these agents is contingent upon compliance with the REMS requirements and enrollment in sponsor programs. It is imperative that advanced oncology practitioners become familiar with the REMS program in order to maintain access to these products and adequately and appropriately manage symptoms. The advanced oncology practitioner is key to furthering the REMS goal: to ensure the safe use of potentially harmful agents.

J Adv Pract Oncol 2011;2:51–57

The Federal Food, Drug, and Cosmetic Act, passed by the United States Congress in 1939, requires a drug's sponsors to provide evidence of the drug's safety prior to marketing approval (Baker, 2009). Since that time, the US Food and Drug Administration (FDA) has been the primary regulatory body that ensures that new medications are adequately tested for safety prior to public release. Over time, the FDA increased its interest in safety after marketing as well. In 2007, risk management became an official process of the FDA. Risk management is considered an ongoing process, with continual assessment of a product's benefit/risk ratio. These quality assessments were traditionally performed by private sponsors and companies, but are now mandated by the FDA. The FDA has the authority to require postmarketing studies and clinical trials and to call for safety-related labeling changes.

Title IX of the 2007 Food and Drug Administration Amendments Act (FDAAA) authorizes the FDA to require drug sponsors to develop and manage a Risk Evaluation and Mitigation Strategy (REMS) for a particular agent with certain safety issues (FDA, 2010). According to the FDA (2010), a REMS is a strategy to manage a potential or known serious risk associated with a drug or biological product. Required by the FDA for certain agents, a REMS is put in place to ensure that a

product's benefits outweigh its risks. A REMS can be required either before a drug is allowed on the market or after product approval for marketing (if new safety information becomes available).

In September 2008, the FDA required 16 products to have a REMS. To date, there are 136 products that require a REMS (FDA, 2010). As of February 2009, the FDA requires classwide REMS programs for controlled-release opioids (such as fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone), citing risks of misuse, abuse, and accidental overdose (American Academy of Pain Medicine, 2009). As of February 2010, a REMS programs are required for erythropoietin-stimulating agents as well (FDA, 2010). As this initiative expands, more drugs and biological agents will be added to list of agents requiring a REMS, which will affect the oncology community and other specialties.

REMS Components

Every REMS program is developed by the individual sponsor of the drug in question. Each sponsor interprets the FDA recommendations and develops the elements that should be included in its REMS program. Hence, there is a lack of standardization between sponsored REMS programs, even between medications in the same class (American Pharmacists Association [APA], 2009). Given the growing number of REMS programs, this will present a significant challenge to health-care providers. A prescriber will need to be familiar with each individual REMS program for many different agents and comply with their requirements in order to prescribe the agent.

There are three possible main components to a REMS: a medication guide or a patient package insert, a communication plan for health-care providers, and an Elements to Assure Safe Use (ETASU)/implementation system (NCCN, 2010). A medication guide is an FDA-approved patient information pamphlet that must be distributed at the time the drug is dispensed (NCCN, 2010). This educational material will address safety issues specific to the drug and drug class, providing information essential for the safe and effective use of that product. A medication guide may be required if certain information is needed to prevent serious adverse effects; if certain safety information is necessary before the patient decides to take the drug; or if there are specific directions to be followed by the patient for safety and efficacy. For example, pazopanib (Votrient) requires a medication guide that is given to the patient when the drug is dispensed, warning of the risk of liver toxicity (FDA, 2010).

A communication plan informs specific audiences (such as prescribers, nurses, pharmacists, health-care facilities, or patients) about both risk and strategies to minimize risk. This plan is usually in the form of a letter. The communication letter may include special educational materials for prescribers to give to patients. An example of a drug with a communication plan is nilotinib (Tasigna; FDA, 2010).

If a REMS requires an ETASU, health-care providers must have certain training (education), experience, or special certification in order to prescribe, dispense, and/or administer the agent. Many oncology prescribers are already familiar with REMS programs that include ETASUs for drugs such as thalidomide (Thalomid) and lenalidomide (Revlimid). Some ETASUs may require patient documentation of certain safe-use conditions, e.g., a negative pregnancy test. Additionally, patients, prescribers, facilities, and/or pharmacies may be required to enroll in a registry. Prescribers may be required to file mandatory, time-sensitive reports of patient responses to treatment. Some REMS programs require drugs to be dispensed only in certain health-care settings, e.g., as certified hospitals, prescribers' offices, or specialty pharmacies.

Not all drugs or biological agents require all three REMS components. Component requirements are based on the severity of the risks and the population likely to be exposed to the product (APA, 2009). The most common REMS programs only require the provision of a medication guide to patients. If the drug is considered to have more serious adverse effects, or a higher risk of abuse or misuse, then the REMS becomes more restrictive. Figure 1 illustrates this concept. The ability to prescribe and dispense certain medications, even some that have been on the market for years, could be contingent upon compliance with REMS provisions (National Comprehensive Cancer Network, 2010).

Monitoring of REMS

The FDA requires all REMS programs to include a timetable for submission of assess-

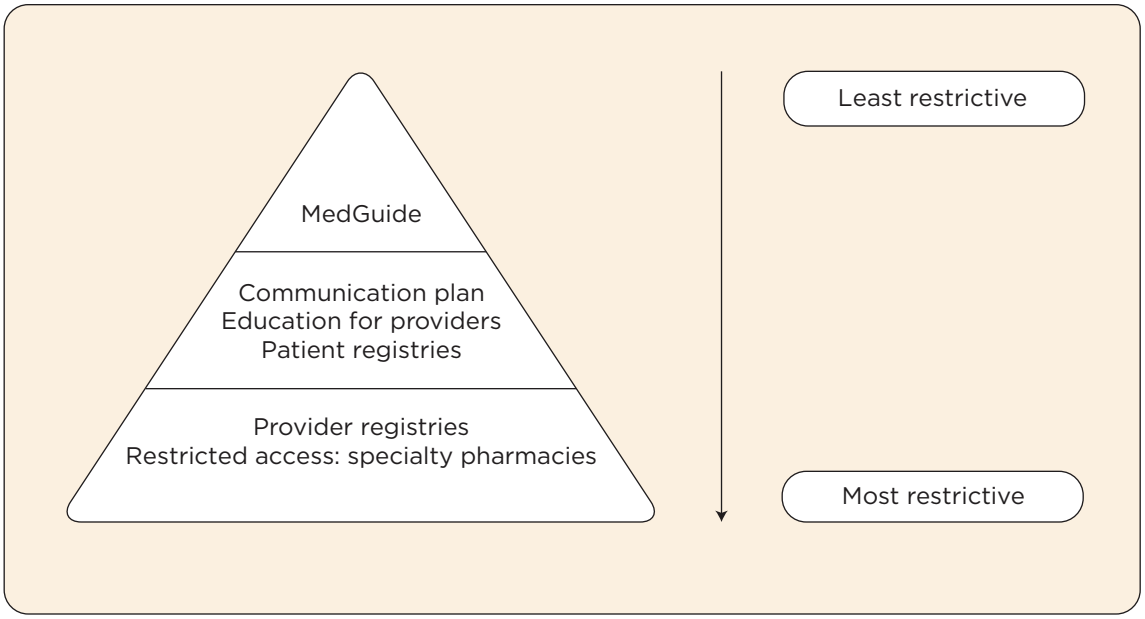

Figure 1. Level of REMS restrictions (least to most restrictive).

Table 1. Intended and Unintended Consequences of a REMS

Intended consequences	Unintended consequences
Reduced diversion of agent	Prescribers reluctant to prescribe agent
Increased appropriate use of agent	Prescribers using a similar agent without REMS
Prescribers/patients more knowledgeable about agent	Fewer patients receiving needed agent or less access to agent
Potential for fewer toxicities/adverse events	Insurance coverage of agent reduced
Facilitates prescriber-patient communication	Increased patient fears and confusion about agents
Provides documentation of need for medication, patient education	Potential stigma of being on a patient registry
Improved understanding of drug and measures for safe use	Increased difficulty in getting a drug to market
Improved informed consent	Delayed or fragmented care
Pharmacies ensure appropriate ordering criteria	Delay in getting medication

Note. Information from AAPM (2009), APA (2009), Baker (2009).

ments of the REMS. Assessments must be conducted periodically beginning at 18 months, followed by 3 years, and 7 years after approval. More frequent assessments may be required. The FDA may eliminate assessments after 3 years if there is a determination that the serious risks associated with the drug are being adequately identified and managed. Both the intended and unintended effects of the REMS (Table 1) are assessed.

Impact on the Prescriber

The intent of a REMS is to provide the prescriber with an organized approach to patient selection. The process will facilitate patient education on medication safety, opening doors of communication between the prescriber and the patient. This education should improve the informed consent procedure. The REMS programs set a new standard of safe care.

As the number of REMS programs increases, the effects will soon be felt by all prescribers. REMS requirements will impact every prescriber in terms of the time investment required to continue prescribing certain agents, as well as changes to the clinical setting's standard operating procedures. There will be financial effects as health-care providers' valuable time is con-

Table 2. Impact of REMS Programs on Prescribers and Patients

Prescribers

Potential positive impact
- Provide an organized approach to patient selection
- Improve prescriber knowledge about medication risks
- Facilitate patient education
- Facilitate prescriber-patient communication
- Provide documentation to support medical recommendations.
- Improve the informed consent procedure
- Improve safe and efficacious use of higher-risk medications

Potential negative impact
- Need to be familiar with training/educational and registry enrollment requirements of each specific REMS
- Changes to standard operating procedures
- Additional patient education requirements
  - Elements of the specific REMS program
  - Balancing of risks and efficacy
- Additional cost
  - Staff training time
  - Prescriber training time
  - Printing and storage of medication guides/forms
  - Storage of REMS materials

Patients

Potential positive impact
- Facilitation of communication with health-care provider
- Improved informed consent with better understanding of risks
- Enhanced patient, caregiver, and family education
- Information provided without pharmaceutical influence
- Increased likelihood that the medication is appropriate for the patient

Potential negative impact
- Complicated process to fill a prescription
- Increased drug costs
- Increased fear of therapy
- Potential to drive patients to less effective options
- Difficulty interpreting information due to:
  - Higher reading levels of many medication guides
  - Language barriers
- Decreased access to certain medications
- Delayed access to certain medications
- Increased need for laboratory testing

sumed with training and educational requirements, patient monitoring reports, additional patient education regarding the REMS, and other aspects of each particular REMS (APA, 2009). The left-hand side of Table 2 identifies both positive and negative potential effects that health-care providers might encounter when enrolling to prescribe a drug that has a REMS.

While not all the possible issues are immediately known, one particular concern about REMS programs is that the information given to the patient does not always provide a balance between safety and efficacy (APA, 2009). While the primary objective of a REMS is to promote the safe use of the product, the product information presented can be frightening and overwhelming to the patient. Balancing patient safety information with efficacy data and providing the individual prescribing rationale is the responsibility of the provider/prescriber. It may require extra time for the prescriber and staff to explain this information.

A second concern, probably more important for prescribers, is the amount of time required to prescribe a medication that has a REMS that includes an ETASU. Table 3 provides a real-life example of the time involved in the prescribing of a drug (eltrombopag [Promacata]) with a REMS that includes an ETASU. In this example, the medication has a REMS requiring prescriber education and a prescriber/patient enrollment registry. The prescriber educational process, a one-time action, required approximately 60 minutes. The physician/patient initial discussion of the drug took about 20 minutes. Patients are required to be enrolled in a registry and sign a consent form, following education. The patient education in this example was performed by the nurse practitioner (although this could have been done by a registered nurse) and required approximately 60 minutes. Some REMS specify that the patient education/discussion must be performed by the prescriber, not a delegate such as a registered nurse.

In the example described in Table 3, the prescriber was required to complete a patient record form first at patient enrollment, periodically throughout treatment, and then again when the drug was discontinued. The patient forms can take about 60 minutes for explanations and documentation. The patient record forms (initial and follow-up) in this example took approximately 100 minutes to complete. This drug has restricted access and must be ordered from a specialty pharmacy. Additional time may be required for seeking financial assistance or obtaining insurance coverage. In this example, seeking insurance

approval was assisted by the specialty pharmacy, but certain forms and information had to be compiled and faxed to the pharmacy, taking an additional 30 minutes. Time is involved in ensuring that required testing (such as periodic pregnancy tests) is performed and that the results meet the standard for drug intake. Completing the drug discontinuation form took approximately 15 minutes. This example described one author's experience with a single patient; more research is needed to determine accurate depictions of time required for specific REMS programs.

As noted in Table 3, the time involved for the prescribing practice could easily be 3 to 5 hours per patient (more time will be required for the initial prescription written for the agent for provider education/enrollment). Most of this time is not reimbursable, with the exception of education/counseling, which can be billed by the physician or advanced oncology practitioner based on the actual amount of face-to-face counseling time.

Finally, medical practices and health-care facilities will now need to budget appropriately for the cost of implementing REMS programs. Additional staff or redistribution of current staff may be necessary. Printing medication guides or required forms and storage of these forms may be needed to comply with regulations, therefore incurring unexpected costs. Computer operating systems or pharmacologic dispensing systems may need modifications. Clinical settings may need to change their current workflow to accommodate the health-care education and documentation.

Table 3. Estimated Time Required to Implement a REMS With an ETASU[a]

Activity time	Time
Initial prescriber enrollment/education	60 min
Prescriber initial discussion with patient	20 min
Education, patient forms/consents	60 min
Baseline safety information form	60 min
Financial assistance/insurance coverage	30 min
Forms every 6 months (estimate: 4 at 10 min each)	40 min
Discontinuation form and notification	15 min
Follow-up discontinuation form	15 min
Estimated time for first patient	**300 min (5 h)**
Estimated time for subsequent patients	**240 min (4 h)**

Note. ETASU = Elements to Assure Safe Use.
[a]This estimate is based on the author's own experience with the prescribing of eltrombopag (Promacta).

Impact on the Patient

Patients will also experience both positive and negative impact from REMS programs. The right-hand side of Table 2 lists some of these potential effects. For the patient, a REMS is intended to provide an organized approach to communication with their health-care provider, facilitating meaningful contact. Required documents will prompt dialog, promote questions, and improve the informed consent. These forms will serve to provide documentation to support the medical recommendations. A REMS should also facilitate patient, caregiver, and family education.

Patients will be affected by REMS programs, as their involvement in the process of obtaining certain prescriptions will change. For some medications, patients will be unable to take a prescription and have it filled at their local pharmacy or walk away without signing consent forms. Concerns regarding possible increased patient costs due to REMS programs may exist. Furthermore, health-care professionals believe that the REMS program will create administrative burdens, disrupt workflow, increase supply costs, and increase health-care provider time, thus shifting more costs to the patients (American Pharmacists Association, 2009).

As mentioned earlier, medication guides often do not balance safety and efficacy for patient understanding. Guides may create unfounded fears and confusion and drive patients to less effective options because of lack of understanding of the materials. The reading level of many medication guides requires a more sophisticated level of understanding than the average patient may possess. Additionally, medication guides may not be available in languages other than English (APA, 2009).

While the patient may be presented information without any pharmaceutical promotional emphasis, patients undergo a more vigorous scrutiny before being prescribed potentially dangerous drugs (Haas, 2009). This process ensures that

the drug is prescribed to the appropriate patient. A consent process will ensure that patients are well aware of and willing to accept the potential risks of a particular medication.

Both access to and timeliness of access to medications are a concern to patients. Drugs that have restricted distribution programs can require patients to obtain their prescriptions from a specialized pharmacy that may not be covered by their current pharmaceutical insurance plan. Access to certain medications could be limited as prescribers may be reluctant to prescribe certain medications because of the restrictions of the REMS programs. There can be delays as insurance concerns are worked out and financial assistance is sought for indigent patients. Required laboratory testing may also delay access to drugs. The Oncology Nursing Society and the American Academy of Pain Medicine have expressed concern that REMS programs must protect patient access to necessary medications, such as pain medications, and not create barriers to relief of chronic cancer pain (American Academy of Pain Medicine, 2009; Oncology Nursing Society [ONS], 2009). The president of the Oncology Nursing Society, Carlton Brown, recently testified before an FDA committee that any opioid REMS program should be reasonable and evidence-based, ensuring that patients with legitimate need have access to the opioid pain therapies that they and their health-care providers deem most appropriate (ONS, 2010).

Table 4. Drugs With REMS Used in the Oncology Setting

Androgel (testosterone) gel[a]
Aranesp (darbepoetin alfa)
Chantix (varenicline)[a]
Darvon capsules, Darvon-N tablets, and Darvocet-N (propoxyphene)[a]
Embeda (morphine sulfate and naltrexone hydrochloride)
Epogen/Procrit (epoetin alfa)
Intron A (interferon alfa-2b)[a]
Metoclopramide oral solution[a]
Morphine sulfate oral solution
Nplate (romiplostim)
Onsolis (fentanyl buccal)
Promacta (eltrombopag)
Reglan ODT (metoclopramide)[a]
Reglan tablets (metoclopramide)[a]
Remicade (infliximab)
Revlimid (lenalidomide)
Tasigna (nilotinib)
Thalomid (thalidomide)
Votrient (pazopanib)[a]
Zyban (buproprion hydrochloride) sustained release tablets[a]

[a]These drug REMS have a medication guide only.

Current Oncologic REMS

There are currently 136 drugs with REMS programs (FDA, 2010). Table 4 lists drugs with REMS programs that are commonly prescribed in the oncologic setting. It is expected that many more REMS programs will be forthcoming, including REMS programs for opioids, and particularly sustained-release agents. The oncology practice and practitioner must be familiar with drugs that require REMS programs. Indications for these agents vary, including growth factors, smoking cessation aids, renal cell carcinoma medications, antiemetic agents, pain medications, and idiopathic thrombocytopenia purpura agents. Each REMS program differs, and prescribers need to be willing to educate themselves in order to provide quality care and symptom management.

Summary

It is imperative that the advanced oncology practitioner keep informed about REMS programs in order to provide quality oncology care (Haas, 2009). While training may be required, the time will be well spent in order to serve oncology patients. Advanced oncology practitioners can take the lead in promoting safe and efficacious use of all oncology therapies. Staff education and training can be a primary concern in daily practice. However, advanced oncology practitioners should continue to voice their concerns and suggestions and offer their clinical expertise to further the ultimate goal of any REMS: to ensure the safe utilization of all medications.

DISCLOSURES

The authors have no conflicts of interest to disclose.

REFERENCES

American Academy of Pain Medicine (AAPM). (2009). Risk Evaluation and Mitigation Strategies (REMS) for opiods; Request for comments (Docket No. FDA-2009-N-0143). Communication to US Food and Drug Administration.

American Pharmacists Association (APA). (2009). White paper on designing a Risk Evaluation and Mitigation Strategies (REMS) system to optimize the balance of patient access, medication safety, and impact on the health care system. Journal of the American Pharmacists Association, 49, 729–743.

Baker, D. (2009). Awareness of Risk Evaluation and Mitigation Strategy program for new drugs. *Hospital Pharmacy, 44*(3):208–209.

United States Food and Drug Administration. (2010). Approved Risk Evaluation and Mitigation Strategies (REMS). Retrieved from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

Haas, M. L. (2009). REMS: An important acronym for nurse practitioners. Paper presented at the Oncology Nursing Society Advanced Practice Nursing Conference, Tampa, FL.

National Comprehensive Cancer Network. (2010). NCCN resource tool: Risk Evaluation and Mitigation Strategies (REMS). Retrieved from http://www.nccn.org/rems/default.asp

Oncology Nursing Society. (2009). Risk Evaluation and Mitigation Strategies for certain opioid drugs: Request for comment (Docket No. FDA-2009-N-0143). Communication to US Food and Drug Administration.

Oncology Nursing Society. (2010). News release: ONS president addresses Food and Drug Administration Committee in Washington on opioid analgesics. Retrieved from http://ons.org/media/ons/docs/newsroom/FDAPressRelease.pdf