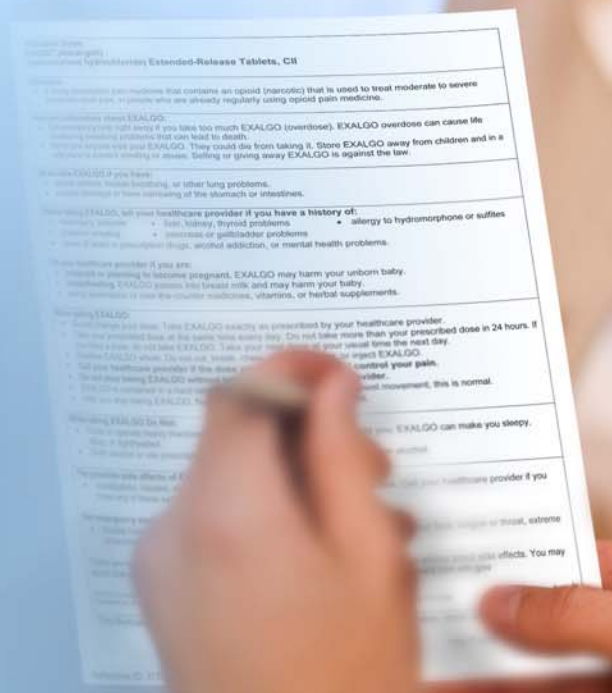
A Brief Overview of

Risk Evaluation & Mitigation Strategies (REMS)



Risk Evaluation and Mitigation Strategies (REMS)

REMS are required risk management plans that use risk minimization strategies beyond the professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks.*

* Authorized by the Food and Drug Administration Amendments Act of 2007 (FDAAA)

Examples of the Types of Risk REMS Requirements Aim to Mitigate*

Risk Example	Possible REMS Action
Serious infection	Patient education of initial warning signs of infection prior to prescribing
Severe allergic reaction	Healthcare professional must be certified to administer the product
Liver damage	Liver function monitoring while the patient is taking the drug
Severe birth defects	Negative pregnancy test prior to dispensing each prescription

* A list of approved REMS is available at:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

REMS : Key Points

- FDA can require a REMS if the agency determines that safety measures are needed beyond the professional labeling to ensure that a drug's benefits outweigh its risks
- Drug sponsors develop REMS programs, FDA reviews and approves them
- FDA can require a REMS before or after a drug is approved
- REMS can be required for a single drug or a class of drugs
- Healthcare professionals and distributors may need to follow specific safety procedures prior to prescribing, shipping, or dispensing the drug
- Each REMS has specific safety measures unique to the safety risks associated with a particular drug or class of drugs (i.e., no two REMS are exactly alike)

Determining when a REMS is needed

- FDA may require a REMS:
  - Before approval: If FDA determines REMS is necessary to ensure that the benefits of the drug outweigh the risk
  - Post-approval: If FDA becomes aware of new safety information* and determines REMS is necessary to ensure that the benefits of the drug outweigh the risks
- The risk must be a serious risk that is documented in the drug's label

* New safety information is defined as a serious risk associated with use of the drug which FDA has become aware since the drug was approved, since a REMS was required, or since the last assessment of the REMS.

Factors considered when determining the need for a REMS

- ☑ Size of the population likely to use the drug
- ☑ Seriousness of the disease
- ☑ Expected benefit of the drug
- ☑ Expected duration of treatment
- ☑ Seriousness of known or potential adverse events
- ☑ Whether the drug is new (i.e., a "new molecular entity" or "NME")

REMS Elements

- All REMS required for an NDA or BLA must contain a timetable for submission of assessments of the REMS
- A REMS for an NDA or BLA may also contain any of the following elements:
  - Medication Guide or Patient Package Insert
  - Communication Plan
  - Elements To Assure Safe Use (ETASU)
  - Implementation System
- REMS for ANDA (generic) products may contain the following:
  - Medication Guide
  - Elements to Assure Safe Use (ETASU)
  - Implementation System

REMS Element: Medication Guides

- Not usually required as part of a REMS unless the REMS includes ETASU
- Required to be dispensed with the drug
- Written in non-technical language
- Standardized format (font size, headers, etc.)
- Provided in *addition to* general information sheets (Consumer Medication Information or CMI)

Medication Guide
TRADENAME® *<Include phonetic spelling>*
(chemical name) Tablets, CII

TRADENAME is:
- A strong prescription pain medicine that contains an opioid (narcotic) that is used to treat moderate to severe around-the-clock pain.

Important information about TRADENAME:
- Get emergency help right away if you take too much TRADENAME (overdose). TRADENAME overdose can cause life threatening breathing problems that can lead to death.
- Never give anyone else your TRADENAME. They could die from taking it. Store TRADENAME away from children and in a safe place to prevent stealing or abuse. Selling or giving away TRADENAME is against the law.

Do not take TRADENAME if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking TRADENAME, tell your healthcare provider if you have a history of:
- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:
- **pregnant or planning to become pregnant.** TRADENAME may harm your unborn baby.
- **breastfeeding.** TRADENAME passes into breast milk and may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements.

When taking TRADENAME:
- Do not change your dose. Take TRADENAME exactly as prescribed by your healthcare provider.
- Take X dose at the same time every day. Do not take more than X dose in XX hours. If you miss a dose, do not take TRADENAME. Take your next dose at your usual time the next day.
- Swallow TRADENAME whole. Do not cut, break, chew, crush, dissolve, or inject TRADENAME.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking TRADENAME without talking to your healthcare provider.**
- After you stop taking TRADENAME, flush any unused *[insert dosage form i.e. tablet or patch]* down the toilet.

While taking TRADENAME Do Not:
- Drive or operate heavy machinery, until you know how TRADENAME affects you. TRADENAME can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol.

The possible side effects of TRADENAME are:
- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:
- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, or you are feeling faint.

These are not all the possible side effects of TRADENAME. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

This Medication Guide has been approved by the U.S. FDA Issue: DATE

REMS Element: Medication Guides

continued

REMS Element: Communication Plan

A communication plan is developed by the drug's sponsor to support implementation of an element of the REMS, and can inform key audiences (health care providers) about the risks of the drug. This could include:

- Sending letters to healthcare providers (e.g., Dear Healthcare Provider letters)
- Disseminating information about the REMS to encourage implementation or to explain certain safety measures
- Disseminating information through professional societies about any serious risks of the drug and any measures to assure safe use

A communication plan educates, informs, and raises awareness of risk.

Examples:
REMS with Communication Plans

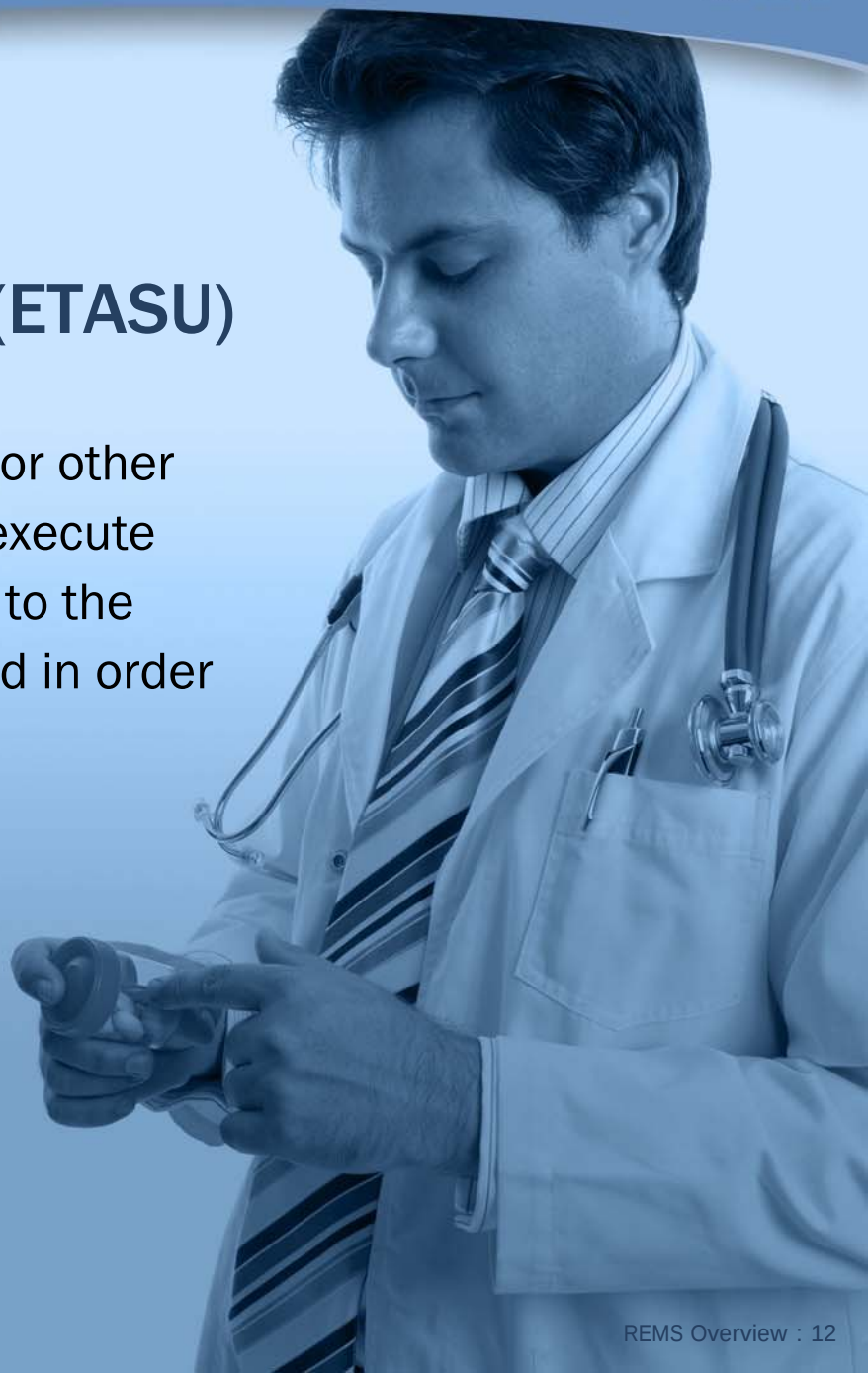
1. **Bydureon (exenatide), a drug to treat type 2 diabetes mellitus:**
   The goal of the REMS is to inform healthcare professionals about the risk of acute pancreatitis and the potential risk of medullary thyroid carcinoma associated with Bydureon.

2. **Potiga (ezogabine), a drug to treat partial-onset seizures:**
   The goal of the REMS is to inform healthcare professionals of the risk of urinary retention and the symptoms of acute urinary retention in patients taking Potiga.

REMS Elements:
Elements to Assure Safe Use (ETASU)

ETASU are required medical interventions or other actions healthcare professionals need to execute prior to prescribing or dispensing the drug to the patient. Some actions may also be required in order for the patient to continue on treatment.

ETASU requirements are the most extensive elements of a REMS program.



REMS Element: Elements To Assure Safe Use (ETASU)

ETASU requirements are intended to reduce a specific serious risk listed in the labeling of the drug.

Depending on the risk, A REMS may require any or all of the following:

- Prescribers have specific training/experience or special certifications
- Pharmacies, practitioners or healthcare settings that dispense the drug be specially certified
- Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals)
- Drug be dispensed with evidence of safe-use conditions such as laboratory test results
- Each patient using the drug be subject to monitoring
- Each patient using the drug be enrolled in a registry

Examples: REMS with ETASU

1. **Caprelsa (vandetanib): drug to treat medullary thyroid cancer**
   - The goal is to educate prescribers and inform patients of the drug's risk of abnormal heart rhythms that can cause sudden death
   - Prescribers must be trained and specially certified
   - Pharmacies must be specially certified

2. **Tysabri (natalizumab): drug to treat multiple sclerosis and Crohn's disease**
   - The goal is to inform prescribers, infusion center healthcare providers, and patients about the risk for progressive multifocal leukoencephalopathy (PML)
   - Prescribers are specially certified
   - Pharmacies and infusion sites are specially certified
   - Evidence of documentation of safe-use conditions

Elements to Assure Safe Use

FDA understands that ETASU should not unduly burden patients, healthcare professionals, or the healthcare system.

The following provisions help ensure REMS are as efficient as possible:

- ETASU requirements must be commensurate with the specific serious risk listed in the drug's labeling
- Cannot be unduly burdensome on patient access to the drug, especially those who have serious or life-threatening diseases and/or difficulty accessing healthcare, and
- To the extent practicable, ETASU must conform with other components for other drugs with similar serious risks and be designed to be compatible with established distribution, procurement, and dispensing systems for drugs.

REMS Element: Implementation System

Implementation system: The drug's sponsor may be required to take reasonable steps to monitor and evaluate those in the healthcare system who are responsible for implementing ETASU measures, if certain ETASU are required.

REMS Component: Timetable for Assessments

- All REMS for NDAs and BLAs must include a timetable for assessing the effectiveness of their safety measures
- Timetable for assessments must be at least by 18 months, 3 years, and in the 7th year after the REMS is approved
- Can be eliminated after 3 years

Assessment results may be used to modify the REMS, or even eliminate it, if the assessment shows changes are needed or that the REMS has met its goals

Assessment Examples: Information Needed

- Survey data: healthcare professionals' understanding regarding the safe use of the drug as measured through surveys
- Summary of adverse events associated with the drug that the REMS was designed to address
- Prescriber compliance with certification and REMS requirements:
  - Completing training and enrollment procedures
  - Completing patient baseline form
  - Complying with discontinuation procedure
- Use data: what patients are getting the drug and under what conditions of use
- Number and percentages of patients who were monitored for potential serious adverse events during treatment with the drug

Examples:
REMS Modified after Assessment

1. **Letairis (ambrisentan), a drug used to treat high blood pressure in the lungs:** Removed requirement for liver function testing.

2. **Promacta (eltrombopag), a drug to treat low blood platelets:** Removed requirements for prescriber, patient, and pharmacy enrollment.

End Note: REMS help keep products on the market

Some drugs would not be able to be approved, or be able to stay on the market, unless a REMS with ETASU was required to ensure that their benefits outweigh their risks.

For more information:

FDA REMS web site

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm

REMS: Moving Forward

- FDA is
  - evaluating how we have been implementing our REMS authority.
  - gathering input from stakeholders about challenges associated with the development and implementation of REMS.
- Our goal is to design REMS that can be better integrated into the existing and evolving healthcare system.
- We welcome input from stakeholders about their experiences with REMS. Please share your comments with our pharmacists in FDA's Division of Drug Information Resources at **druginfo@fda.hhs.gov**.

Thank you!