FDA Drug Topics: Overview of Risk Evaluation and Mitigation Strategies (REMS) for Health Care Providers

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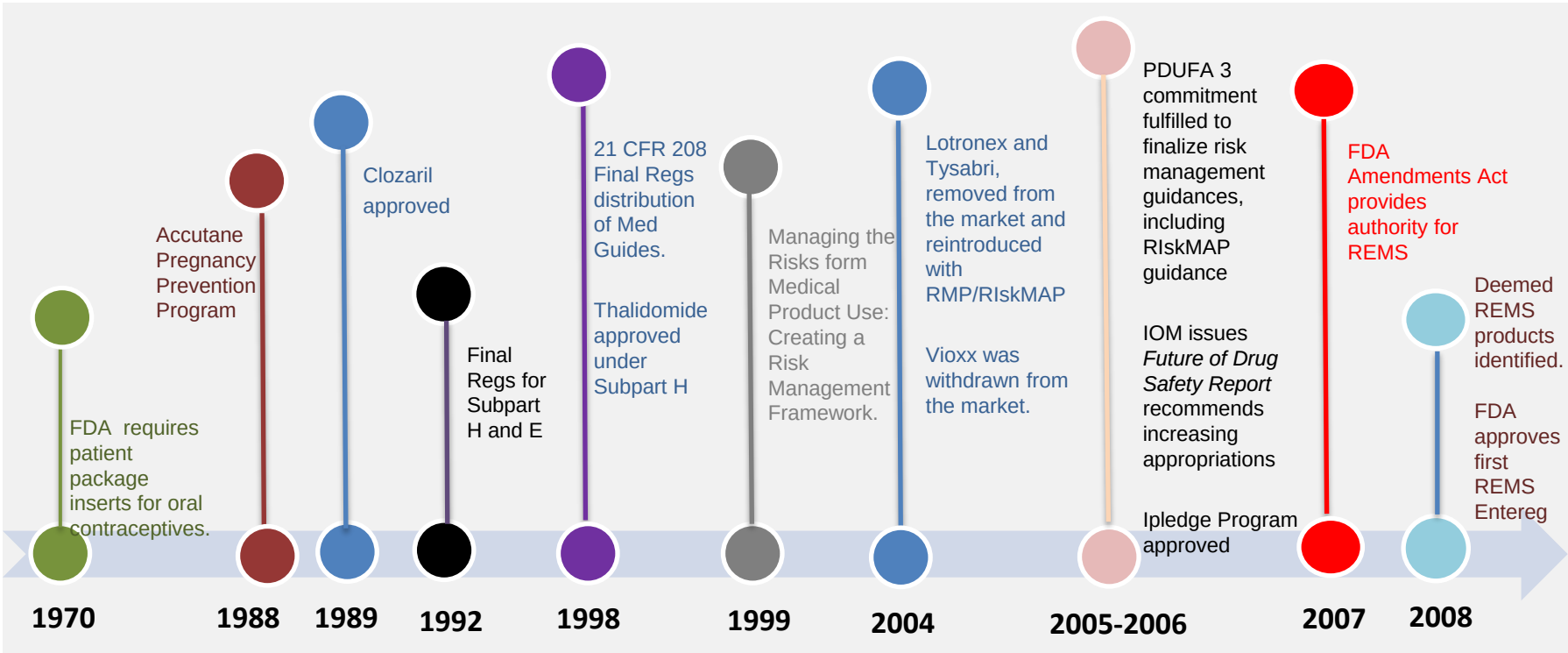
Office of Surveillance & Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration

Learning objectives

- Describe when the FDA can require a REMS
- List the different elements of a Risk Evaluation and Mitigation Strategies
- Identify REMS resources available to healthcare professionals
- Discuss the possible enforcement actions by the FDA

Overview of REMS Authorities

FDA Risk Management Over the Years



Safety issues are typically managed through labeling and post marketing reporting

- Labeling is the cornerstone and the foundation for risk management of FDA-approved products (drugs/therapeutic biologics)
- Routine post marketing reporting requirements allow FDA to continually assess the benefit-risk profile of a drug/therapeutic biologic following FDA approval

Risk Evaluation and Mitigation Strategies (REMS)

- FDA Amendments Act (FDAAA) of 2007 authorized FDA to require sponsors to develop and comply with REMS programs if determined necessary to ensure the benefits outweigh the risks.
- REMS are risk management plans that uses risk minimization strategies beyond professional labeling.
- REMS are designed to achieve specific goals to mitigate risks associated with use of a drug.
- REMS can be required preapproval if necessary to ensure the benefits outweigh the risks or post-approval if FDA becomes aware of new safety information.
- Applies to NDAs, BLAs and ANDAs

Updates to 2007 REMS Authorities

- July 2012 - FDA Safety and Innovation Act (FDASIA)
- December 2016 - 1st Century Cures Act
- October 2018 - Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act
- Appropriations Act of 2020

Introduction to REMS

REMS are required risk management programs

REMS provide safe access for patients to drugs with known serious risks that would otherwise be unavailable.

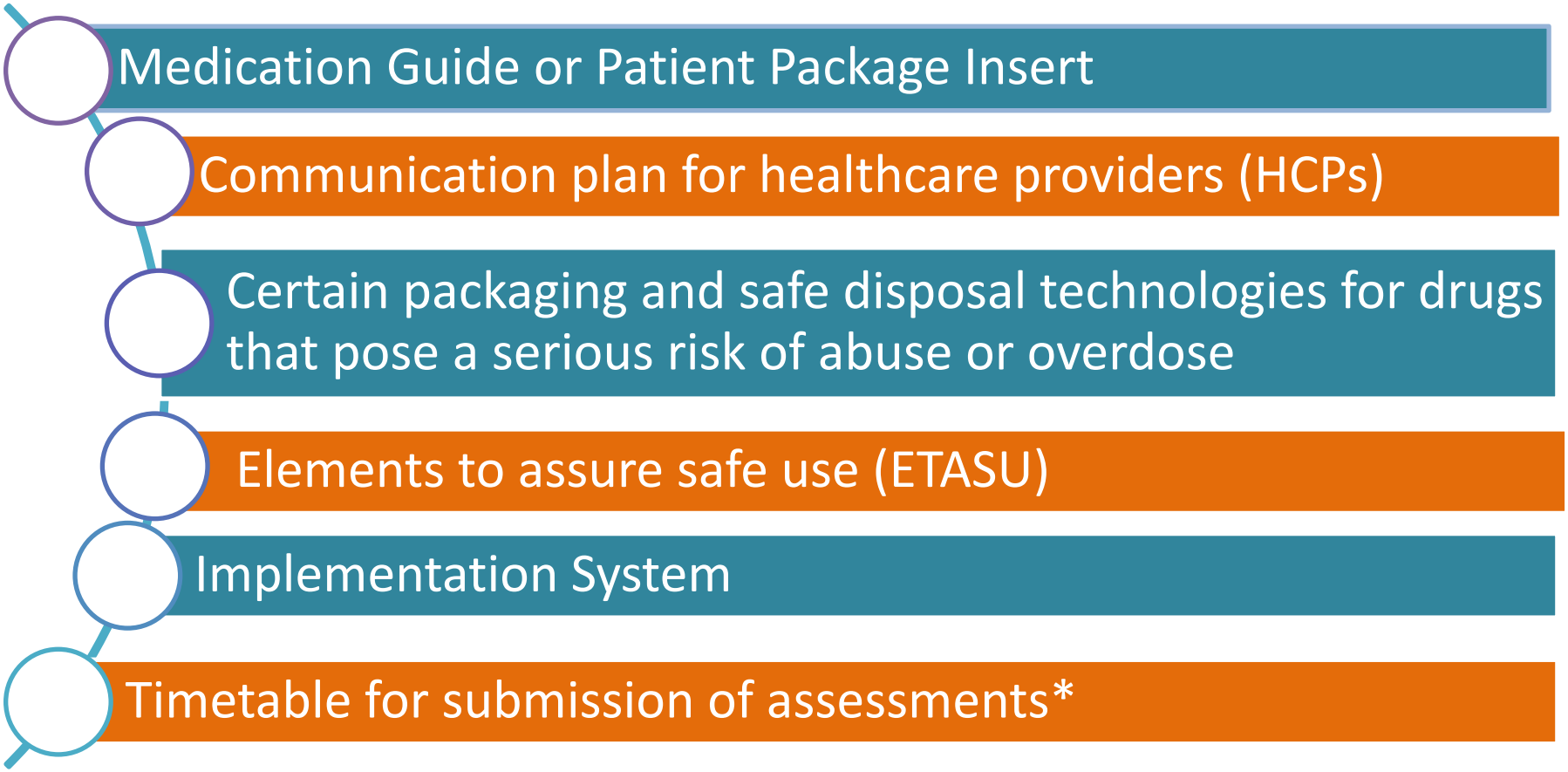
REMS are not designed to mitigate all the adverse events of a medication.

They focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event.

Statutory factors for determination of a REMS as stated in FDAAA

- Estimated size of the population likely to use the drug
- Seriousness of the disease or condition to be treated
- Expected benefit of the drug
- Duration of treatment with the drug
- Seriousness of any known or potential adverse effects related to the use of drug and background rate of such events in population likely to use the drug
- Whether a drug is a new molecular entity (NME)

Possible Elements of a REMS



**Note: This requirement applies to NDAs and BLAs only. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS*

REMS Communication Plan

- **Include FDA approved materials**
- Can be used to aid in the implementation of the REMS
- Inform healthcare providers about serious risks
  - Dissemination of safety information to healthcare providers or through professional societies
  - Cannot be directed to patients

A REMS can include one or more the following ETASU

- Prescribers have specific training/experience or special certifications
- Pharmacists or other dispensers 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 result
- Each patient using the drug be subject to monitoring
- Each patient using the drug be enrolled in a registry

Are not mutually exclusive and are often used in combination to create a risk management program

REMS and Generics

Generic product (ANDA) referencing a drug with a REMS is subject to these components of the REMS:

- Med Guide or patient package insert (PPI)

-Elements to Assure Safe Use (ETASU)

For ETASU, the ANDA may use a single, shared system with the reference list drug; or a different, comparable aspect of the ETASU

*Uses different methods or operational means than the REMS for the listed drug; but achieves the same level of safety.

Shared System REMS

For REMS that include ETASU

- Development of a shared system REMS is encouraged between products that are submitted for approval or licensure based on the reference listed drug.

Benefits of a Share System REMS

Reduces burden for different stakeholders

- Provides a single portal to access materials and provide documentation
- Prescribers, pharmacies, and healthcare settings complete certification and other administrative requirements

Potential for cost sharing among all sponsors

Shared system REMS for subsequent products

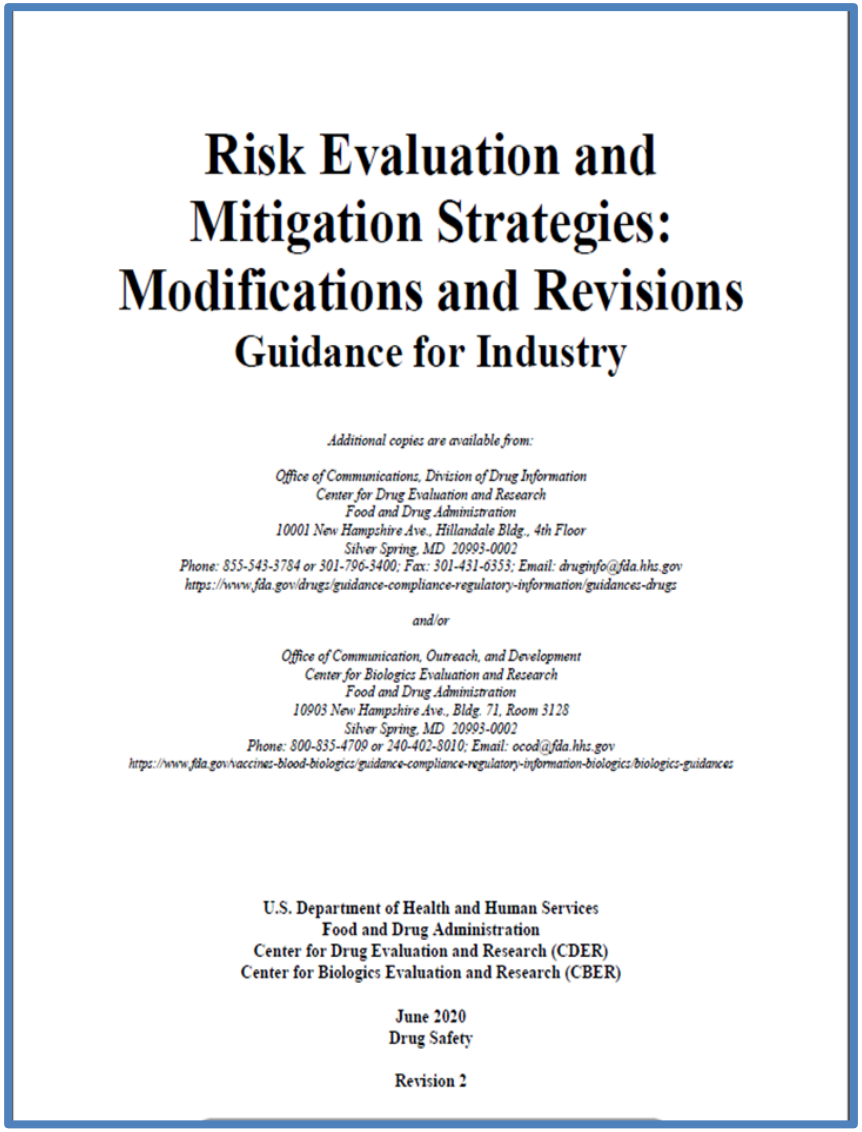
- If FDA approves a separate REMS for a product that is based on the reference listed drug, it can require that this separate REMS be open to any other products for same reference listed drug.

- Avoids the multiple REMS for the same drug.

Single shared system can be required in some cases

- FDA can still require use of a single shared system REMS if it determines that no different, comparable aspect of the [ETASU] could satisfy the requirements.

REMS Modifications



Risk Evaluation and Mitigation Strategies: Modifications and Revisions

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

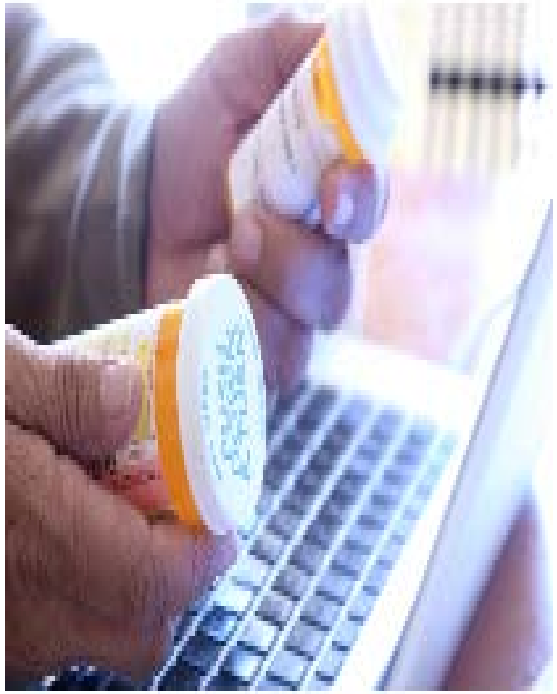
June 2020
Drug Safety

Revision 2

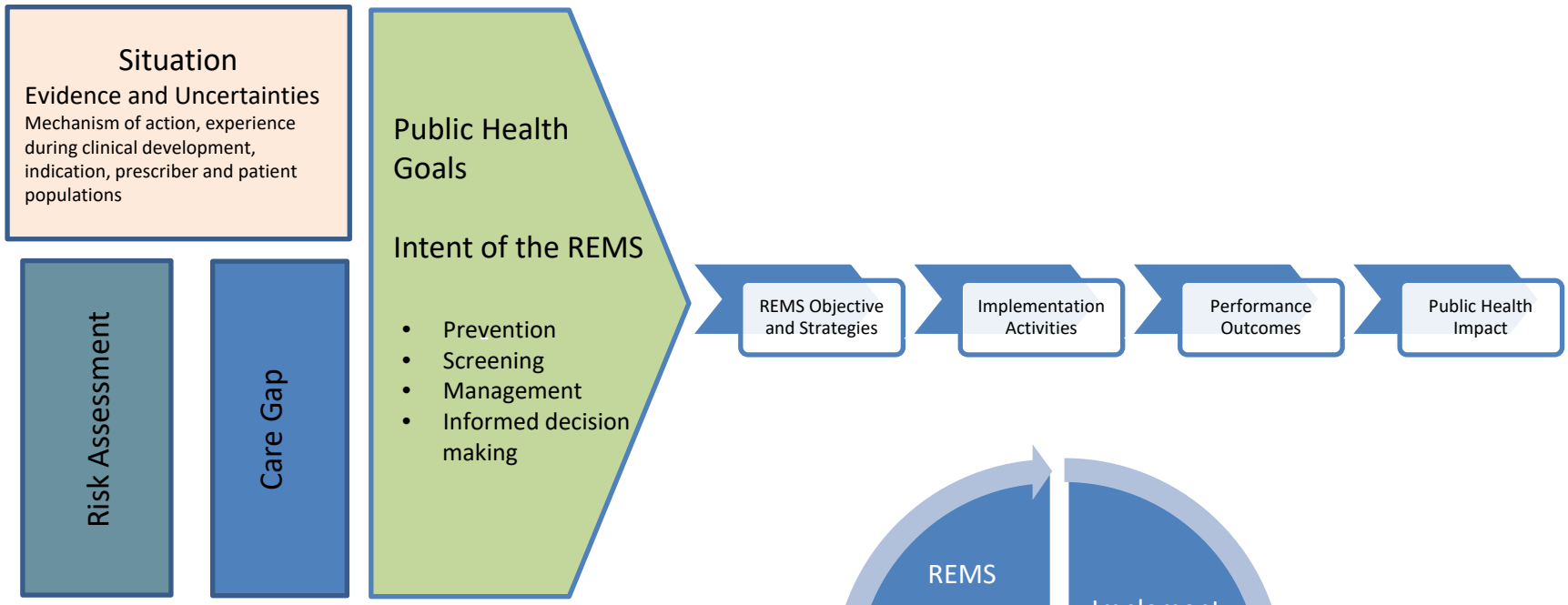
- Applicants can propose a modification to their REMS- at any time.
- FDA can require a REMS Modification
  - Ensure the benefits of the drug outweigh the risks;
  - Minimize the burden on the healthcare delivery system; **or**
  - To accommodate different, comparable aspects of ETASU for an ANDA and the reference list drug.

Possible reasons for REMS modifications

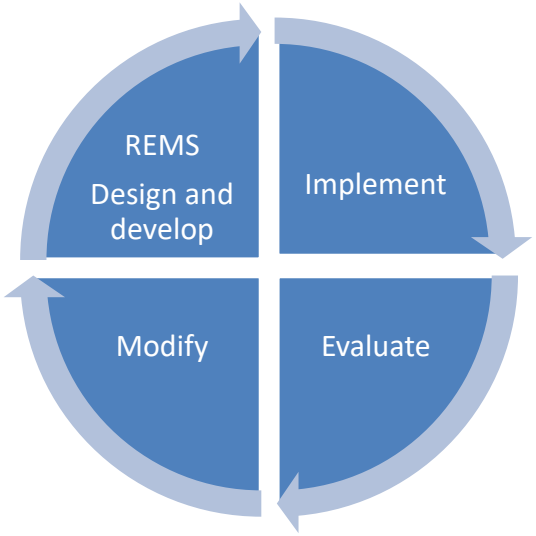
- Efficacy supplement
  - New indication for product has a different benefit/risk balance
  - Safety labeling changes
- Modification to reduce burden
- REMS certain REMS activities concluded
- Goal not being met
- All or certain REMS requirements are no longer necessary to ensure the benefits outweigh the risks



Considerations for REMS Design



Adapted from Morrato, Toyserkani, Huynh (*ICPE All Access 2020*)



Assessing REMS

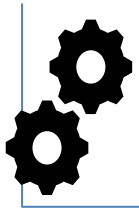
Assessment Categories

Program Outreach and Communication

Measures of the extent to which the REMS materials reached the intended stakeholders

Program Implementation and Operations

Measures of the extent to which the intended stakeholders are participating in the program; how effectively the REMS program is being implemented and any unintended consequences such as patient access or burden to the healthcare system

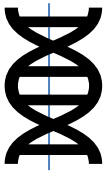


Knowledge

Measures of the extent of stakeholders' knowledge about the REMS-related risk or knowledge of any safe use conditions

Safe Use Behaviors

Measures of the extent to which safe use conditions are being adopted or followed

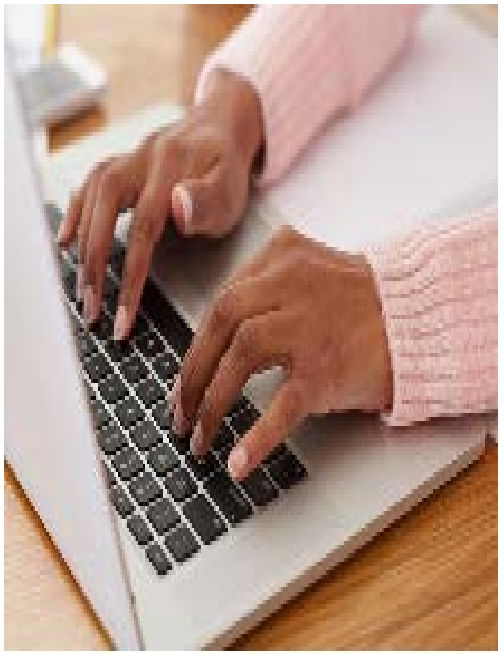


Health Outcomes and/or Surrogates of Health Outcomes

Measures of the safety-related health outcome of interest or a surrogate of a health outcome

Potential challenges with REMS Assessments

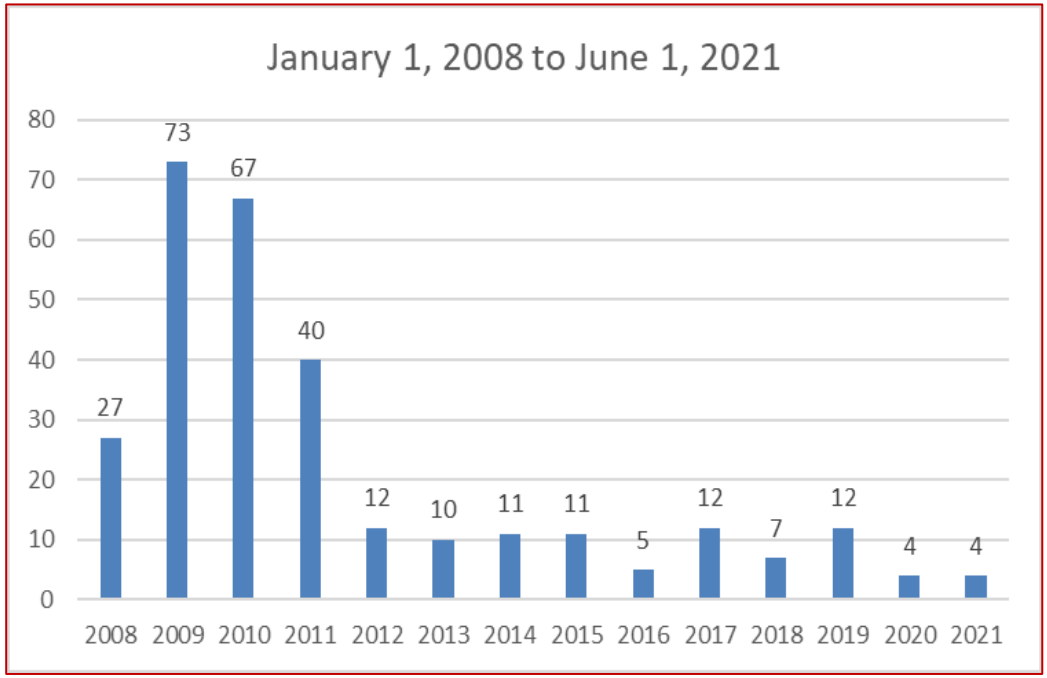
- Lack of baseline data
- Performance thresholds maybe difficult to establish
- The impact of the REMS maybe confounded by other healthcare or public health initiatives
- Available data sources may provide insufficient information in some cases
- Serious but rare events
- Stakeholder populations maybe small



REMS Approved by calendar year

Jan 2008 – June 1, 2021

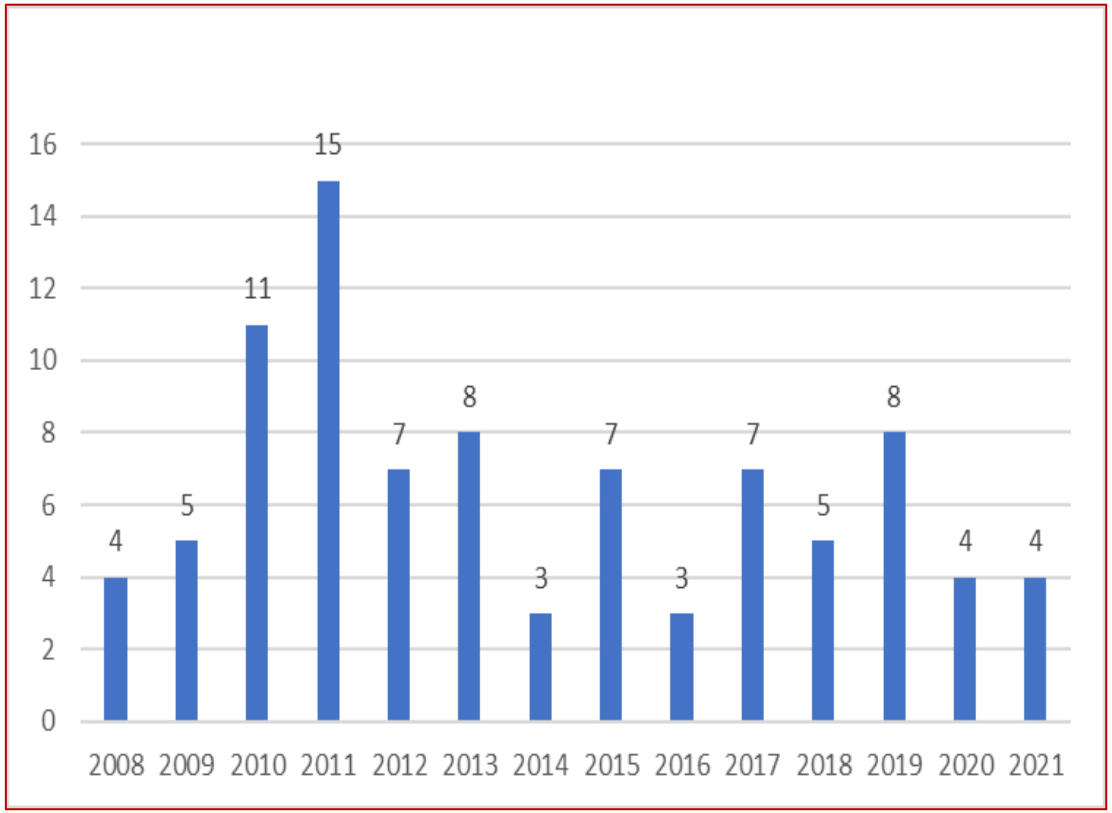
- FDA has approved a total of 295 REMS
- 61 are currently active
- The majority of the REMS approved in 2009-2011 were Medication Guide only REMS



REMS approved with ETASU

Jan 2008 – June 1, 2021

- FDA has approved a total of 91 REMS ETASU
- Currently 55 REMS with ETASU are active



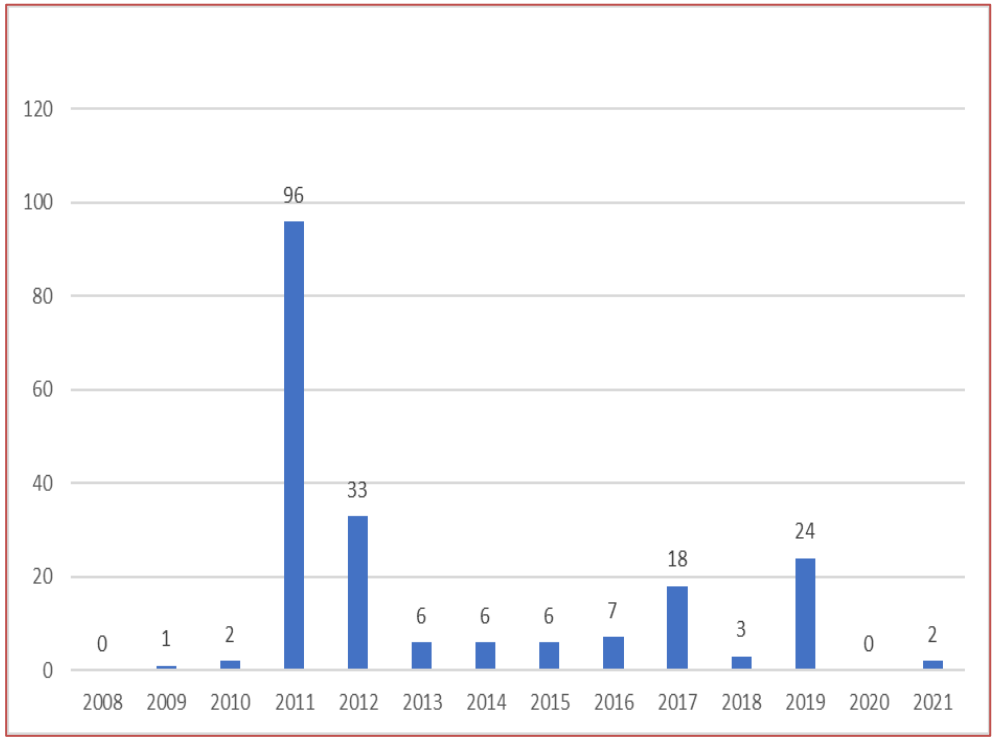
REMS that have been released

Jan 2008 – June 1, 2021

A total of 204 have been released

Of those

- 138 Medication Guide only REMS
- 58 Communication Plans +/- Medication Guide
- 8 REMS with ETASU



Information for healthcare providers about REMS

Where can health providers find information about REMS?

- REMS Document/REMS Materials
- REMS@FDA Website
- Risk Evaluation and Mitigation Strategies (REMS) Resource Web Page
- FDA Guidance on REMS
- Manufacturer REMS Websites

Stakeholder Feedback

- Requirements are not communicated in a clear and consistent manner
- Unclear who is responsible for implementing each REMS requirement
- Too much time spent trying to understand and comply with REMS
- Difficult to integrate REMS into existing health information systems and health care delivery processes

2017 Draft Guidance for Industry – Format and Content of a Document on REMS

REMS Document

I. Administrative Information
II. REMS Goals
III. REMS Requirements
   - Section A: REMS *Participant* Requirements
     - Healthcare providers who prescribe
     - Patients who are dispensed
     - Healthcare settings/prescribers/pharmacies that dispense
     - Wholesalers that distribute
   - Section B: REMS *Applicant* Requirements
     - Training
     - Communication
     - Operations
     - Compliance
IV. REMS Assessment –Timetable for submission of assessments
V. REMS Materials

2017 Draft - Format and Content of a REMS Document

Standardize concepts
Communicated clearly the requirements for each stakeholder

The "4 W" of
the REMS Document

This is the key organizational principle serving as the foundation for how REMS information is organized in the REMS document template.

REMS @FDA website uses a similar format.

"W"	Description	Examples
"Who"	The participant who must meet the REMS requirement	prescriber, dispenser, health care setting
"When"	A particular "stage" in the treatment or medication use process around which REMS activities needs to occur	certification, prescribing, dispensing, administration
"What"	a clinical or administrative activity that must be performed as part of the REMS	counseling a patient, completing an enrollment form, lab testing
"With What"	Approved REMS material with which the requirement is carried out	enrollment form, medication guide, educational pamphlet

Fintepla (fenfluramine)

Indication: for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older

Risks: valvular heart disease and pulmonary arterial hypertension

Risk Mitigation: patients must be monitored with an echocardiogram (ECHO) to identify valvular heart disease

REMS Document

Fintepla (fenfluramine)

III. REMS Requirements

Zogenix, Inc. must ensure that healthcare providers, patients, pharmacies, and wholesaler-distributors comply with the following requirements:

Who

1. Healthcare providers who prescribe FINTEPLA must:	
To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the following: Prescriber Training and REMS Program Overview. 3. Successfully complete the Prescriber Knowledge Assessment and submit it to the REMS Program. 4. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.

With What

Reference ID: 4631810

When

1. Healthcare providers who prescribe FINTEPLA must:	
Before treatment initiation (first dose)	5. Counsel the patient on the risks of valvular heart disease and pulmonary arterial hypertension, including how to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension, and the need for cardiac monitoring via echocardiogram at baseline (treatment initiation), every 6 months during treatment, and once 3 to 6 months after treatment discontinuation using the Patient Guide. 6. Provide the patient with the Patient Guide. 7. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS. 8. Assess the patient's cardiovascular status and the appropriateness of initiating treatment by obtaining an echocardiogram. Document and submit the results and authorization for treatment to the REMS Program using the Patient Status Form.
During treatment: Every 6 months	9. Counsel the patient on the need for cardiac monitoring via echocardiogram every 6 months during treatment using the Patient Guide. 10. Assess the patient's cardiovascular status and the appropriateness of continuing treatment by obtaining an echocardiogram. Document and submit the results and appropriateness of continued treatment to the REMS Program using the Patient Status Form.
After treatment discontinuation: 3 to 6 months	11. Assess the patient's cardiovascular status by obtaining an echocardiogram. Document and submit the results to the REMS Program using the Patient Status Form.
At all times	12. Report adverse events suggestive of valvular heart disease and/or pulmonary arterial hypertension on the Cardiovascular Adverse Event Reporting Form to the REMS Program. 13. Report treatment discontinuation or transfer of care to the REMS Program.

What

Fintepla (fenfluramine)

REMS materials are reviewed and approved by the Agency as part of the REMS.

V. REMS Materials

The following materials are part of the FINTEPLA REMS:

Enrollment Forms

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharmacy:

3. Outpatient Pharmacy Enrollment Form
4. Inpatient Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

5. Prescriber Training
6. REMS Program Overview
7. Prescriber Knowledge Assessment

Patient:

8. Patient Guide

Pharmacy:

9. Pharmacy Guide
10. REMS Program Overview

Patient Care Forms

11. Patient Status Form
12. Cardiovascular Adverse Event Reporting Form

Communication Materials

13. Letter for Healthcare Providers

Other Materials

14. REMS Website

REMS Communication and Training/Educational Materials

- Dear Healthcare Provider Letters
- REMS fact sheet
- REMS-dedicated websites
- Informational slide deck/webinars
- Journal information pieces
- Patient counseling tools
- Training programs
- Informational brochures
- REMS call center
- Wallet card
- Patient-provider acknowledgements
- Prescription authorization forms
- Enrollment forms (prescriber, pharmacist, patient)

REMS Communicatio
Training/Educational

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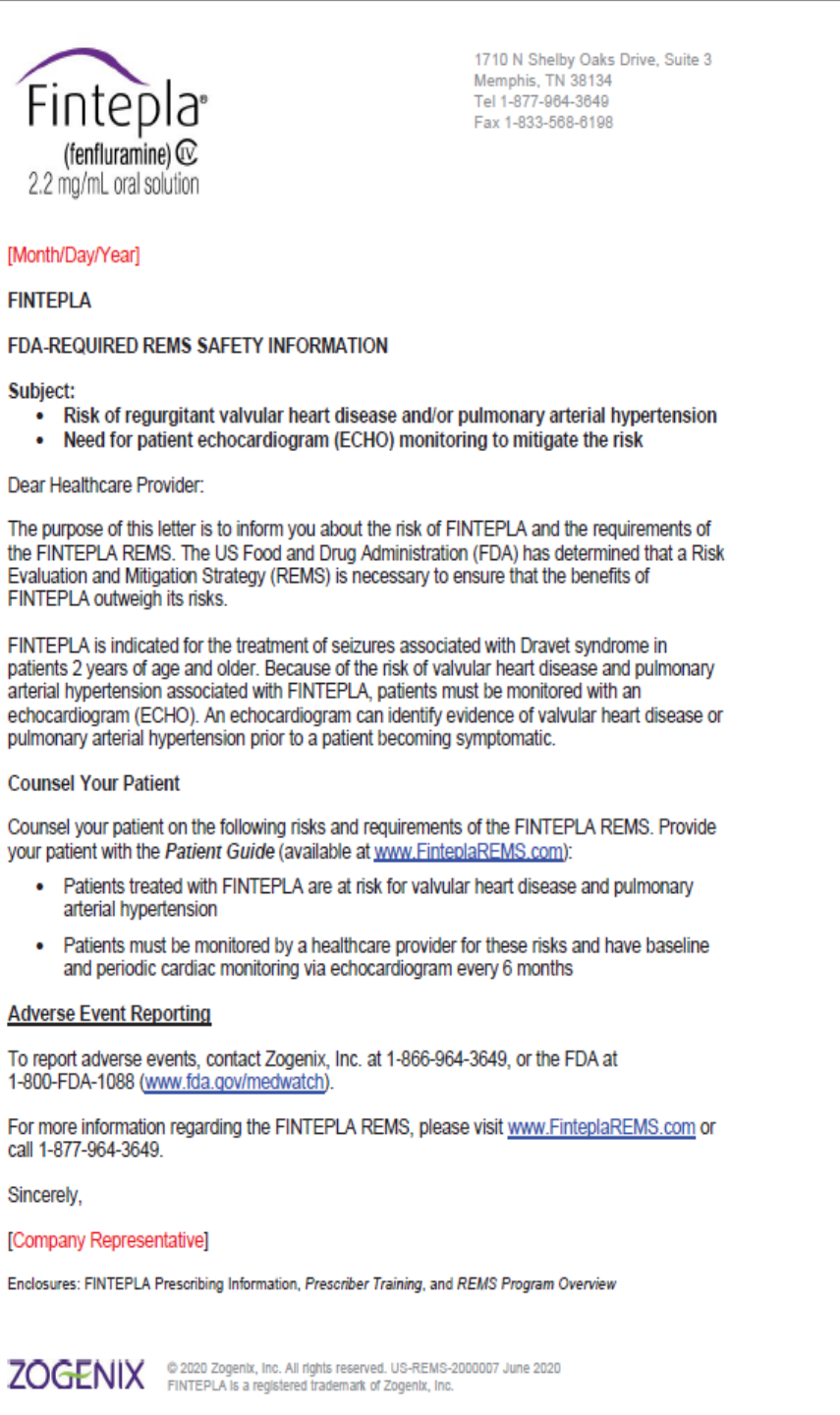

Fintepla®
(fenfluramine) CV
2.2 mg/mL oral solution

1710 N Shelby Oaks Drive, Suite 3
Memphis, TN 38134
Tel 1-877-964-3649
Fax 1-833-568-6198

[Month/Day/Year]

FINTEPLA

FDA-REQUIRED REMS SAFETY INFORMATION

Subject:
- **Risk of regurgitant valvular heart disease and/or pulmonary arterial hypertension**
- **Need for patient echocardiogram (ECHO) monitoring to mitigate the risk**

Dear Healthcare Provider:

The purpose of this letter is to inform you about the risk of FINTEPLA and the requirements of the FINTEPLA REMS. The US Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of FINTEPLA outweigh its risks.

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. Because of the risk of valvular heart disease and pulmonary arterial hypertension associated with FINTEPLA, patients must be monitored with an echocardiogram (ECHO). An echocardiogram can identify evidence of valvular heart disease or pulmonary arterial hypertension prior to a patient becoming symptomatic.

Counsel Your Patient

Counsel your patient on the following risks and requirements of the FINTEPLA REMS. Provide your patient with the *Patient Guide* (available at www.FinteplaREMS.com):

- Patients treated with FINTEPLA are at risk for valvular heart disease and pulmonary arterial hypertension
- Patients must be monitored by a healthcare provider for these risks and have baseline and periodic cardiac monitoring via echocardiogram every 6 months

Adverse Event Reporting

To report adverse events, contact Zogenix, Inc. at 1-866-964-3649, or the FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

For more information regarding the FINTEPLA REMS, please visit www.FinteplaREMS.com or call 1-877-964-3649.

Sincerely,

[Company Representative]

Enclosures: FINTEPLA Prescribing Information, *Prescriber Training*, and *REMS Program Overview*

ZOGENIX

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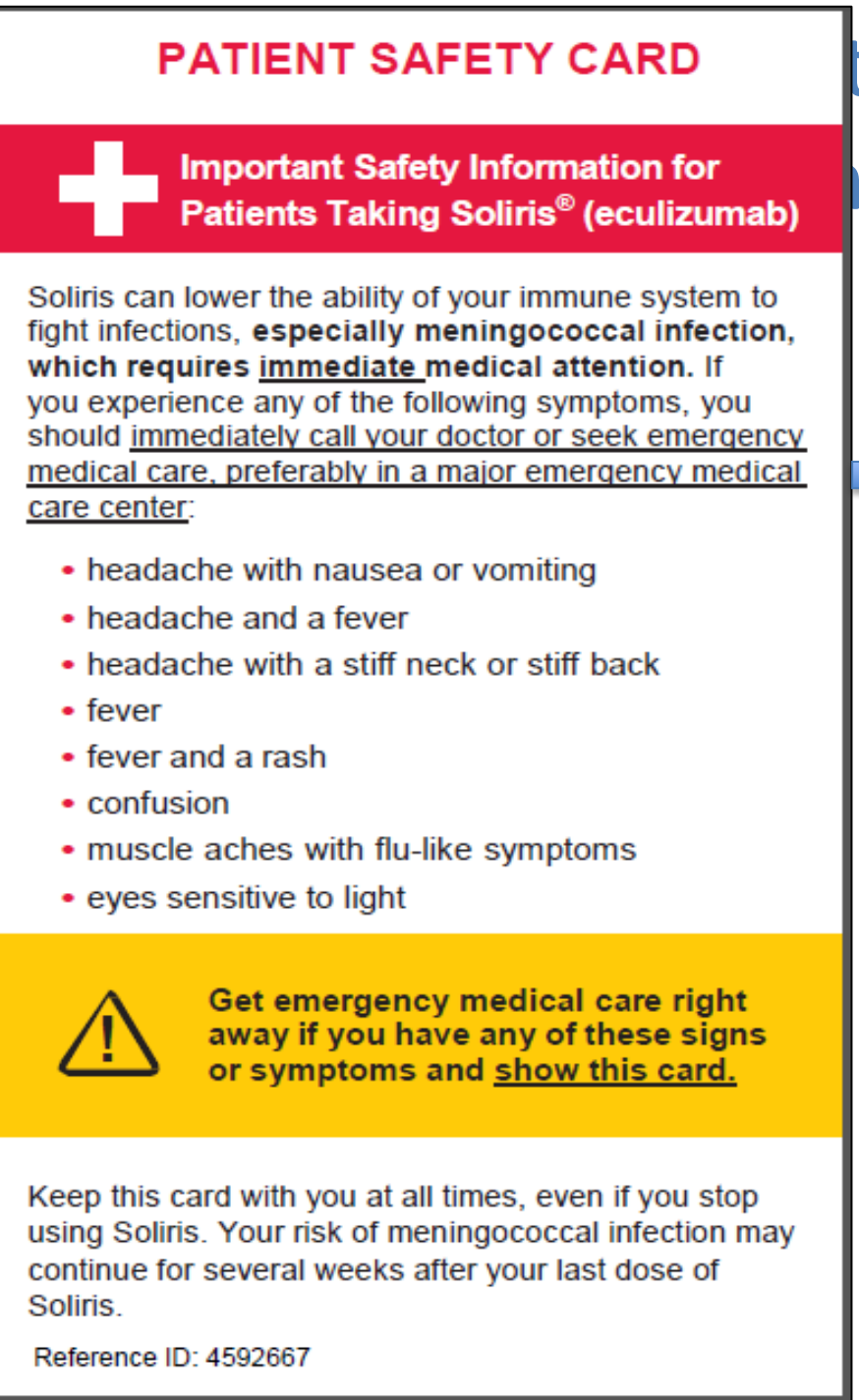
al Materials



PATIENT SAFETY CARD

Important Safety Information for Patients Taking Soliris® (eculizumab)

Soliris can lower the ability of your immune system to fight infections, **especially meningococcal infection, which requires immediate medical attention.** If you experience any of the following symptoms, you should immediately call your doctor or seek emergency medical care, preferably in a major emergency medical care center:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Get emergency medical care right away if you have any of these signs or symptoms and show this card.

Keep this card with you at all times, even if you stop using Soliris. Your risk of meningococcal infection may continue for several weeks after your last dose of Soliris.

Reference ID: 4592667

- REMS Call Center
- Wallet Card
- Patient-Provider Acknowledgements
- Prescription Authorization Forms
- Enrollment forms (prescriber, pharmacist, patient)

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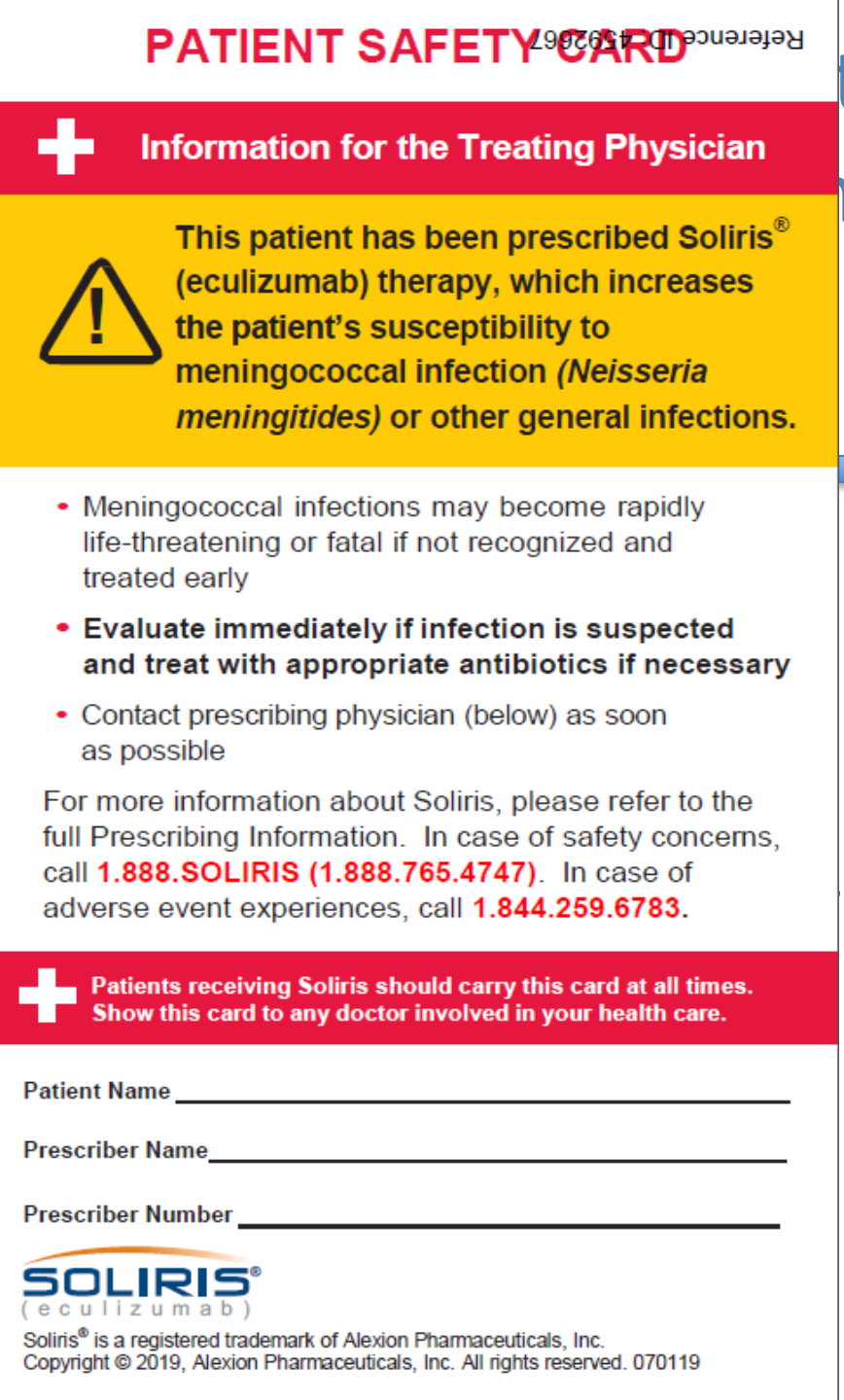

PATIENT SAFETY CARD

Reference ID: 4592867

Information for the Treating Physician

This patient has been prescribed Soliris® (eculizumab) therapy, which increases the patient's susceptibility to meningococcal infection *(Neisseria meningitides)* or other general infections.

- Meningococcal infections may become rapidly life-threatening or fatal if not recognized and treated early
- **Evaluate immediately if infection is suspected and treat with appropriate antibiotics if necessary**
- Contact prescribing physician (below) as soon as possible

For more information about Soliris, please refer to the full Prescribing Information. In case of safety concerns, call 1.888.SOLIRIS (1.888.765.4747). In case of adverse event experiences, call 1.844.259.6783.

Patients receiving Soliris should carry this card at all times. Show this card to any doctor involved in your health care.

Patient Name _____

Prescriber Name _____

Prescriber Number _____

SOLIRIS® (eculizumab)

Soliris® is a registered trademark of Alexion Pharmaceuticals, Inc.

- REMS Call Center
- Wallet Card
- Patient-Provider Acknowledgements
- Prescription Authorization Forms
- Enrollment forms (prescriber, pharmacist, patient)

REMS Communicat
Training/Education

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What You Need to Know About Opioid Pain Medicines

This guide is for you! Keep this guide and the Medication Guide that comes with your medicine so you can better understand what you need to know about your opioid pain medicine. Go over this information with your healthcare provider. Then, ask your healthcare provider about anything that you do not understand.

What are opioids?

Opioids are strong prescription medicines that are used to manage severe pain.

What are the serious risks of using opioids?

- Opioids have serious risks of addiction and overdose.
- **Too much opioid medicine in your body can cause your breathing to stop – which could lead to death.** This risk is greater for people taking other medicines that make you feel sleepy or people with sleep apnea.
- **Addiction** is when you crave drugs (like opioid pain medicines) because they make you feel good in some way. You keep taking the drug even though you know it is not a good idea and bad things are happening to you. Addiction is a brain disease that may require ongoing treatment.

Risk Factors for Opioid Abuse:

- You have:
  - a history of addiction
  - a family history of addiction
- You take medicines to treat mental health problems
- You are under the age of 65 (although anyone can abuse opioid medicines)

- **You can get addicted to opioids even though you take them exactly as prescribed, especially if taken for a long time.**
- If you think you might be addicted, talk to your healthcare provider right away.
- If you take an opioid medicine for more than a few days, your body becomes physically "dependent." This is normal and it means your body has gotten used to the medicine. You must taper off the opioid medicine (slowly take less medicine) when you no longer need it to avoid withdrawal symptoms.

How can I take opioid pain medicine safely?

- Tell your healthcare provider about all the medicines you are taking, including vitamins, herbal supplements, and other over-the-counter medicines.
- Read the Medication Guide that comes with your prescription.
- Take your opioid medicine exactly as prescribed.
- Do not cut, break, chew, crush, or dissolve your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- When your healthcare provider gives you the prescription, ask:
  - How long should I take it?
  - What should I do if I need to taper off the opioid medicine (slowly take less medicine)?
- Call your healthcare provider if the opioid medicine is not controlling your pain. Do not increase the dose on your own.
- Do not share or give your opioid medicine to anyone else. Your healthcare provider selected this opioid and the dose just for you. A dose that is okay for you could cause an overdose and death for someone else. Also, it is against the law.
- Store your opioid medicine in a safe place where it cannotbe reached by children or stolen by family or visitors to your home. Many teenagers like to experiment with pain medicines. Use a lock- box to keep your opioid medicine safe. Keep track of the amount of medicine you have.

- Do not operate heavy machinery until you know how your opioid medicine affects you. Your opioid medicine can make you sleepy, dizzy, or lightheaded.

What should I avoid taking while I am taking opioids?

Unless prescribed by your healthcare provider, you should avoid taking alcohol or any of the following medicines with an opioid because it may cause you to stop breathing, which can lead to death:

- Alcohol: Do not drink any kind of alcohol while you are taking opioid medicines.
- Benzodiazepines (like Valium or Xanax)
- Muscle relaxants (like Soma or Flexeril)
- Sleep medicines (like Ambien or Lunesta)
- Other prescription opioid medicines

REMS Communica
Training/Educatio

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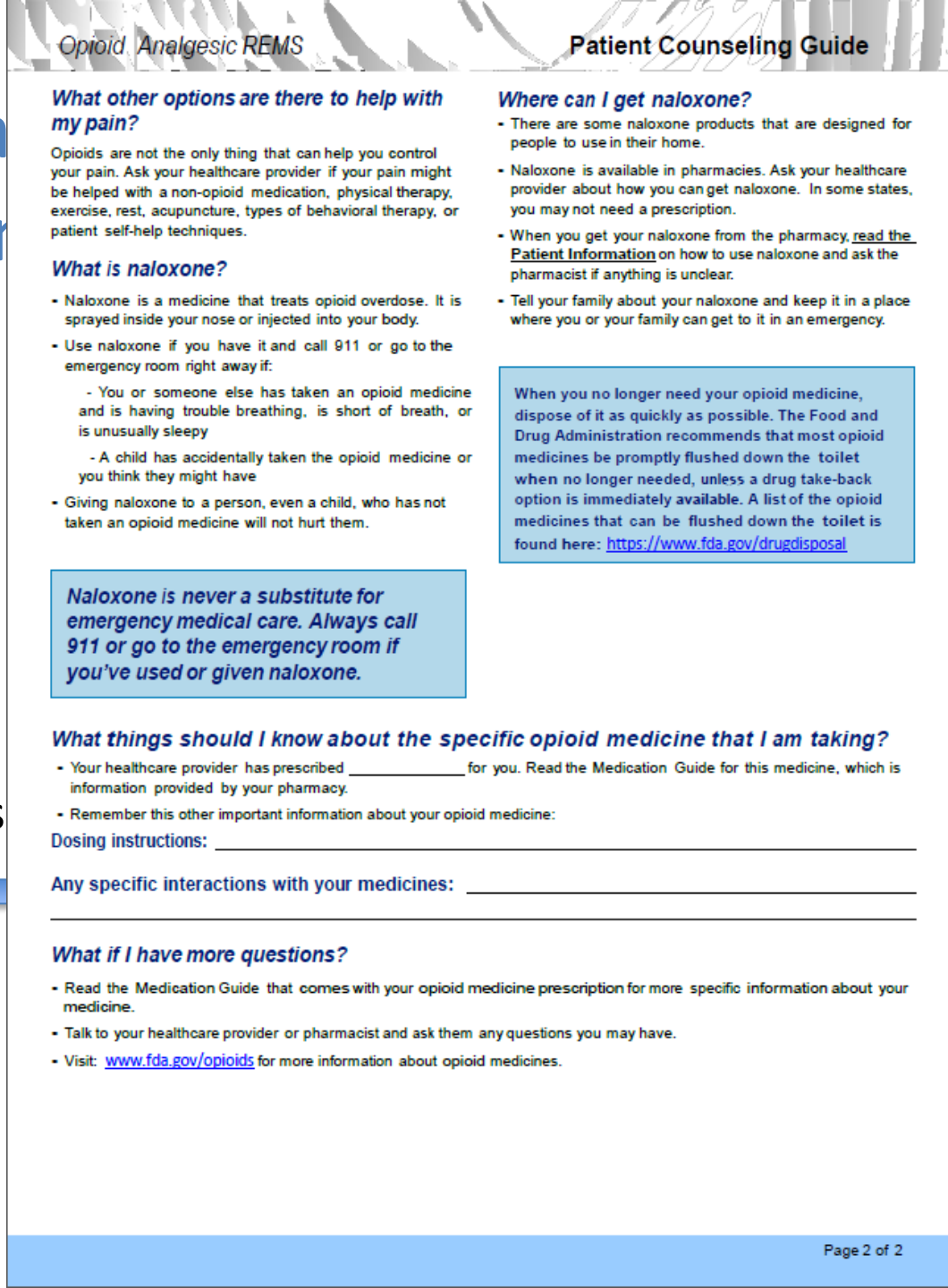


What other options are there to help with my pain?

Opioids are not the only thing that can help you control your pain. Ask your healthcare provider if your pain might be helped with a non-opioid medication, physical therapy, exercise, rest, acupuncture, types of behavioral therapy, or patient self-help techniques.

What is naloxone?

- Naloxone is a medicine that treats opioid overdose. It is sprayed inside your nose or injected into your body.
- Use naloxone if you have it and call 911 or go to the emergency room right away if:
  - You or someone else has taken an opioid medicine and is having trouble breathing, is short of breath, or is unusually sleepy
  - A child has accidentally taken the opioid medicine or you think they might have
- Giving naloxone to a person, even a child, who has not taken an opioid medicine will not hurt them.

Naloxone is never a substitute for emergency medical care. Always call 911 or go to the emergency room if you've used or given naloxone.

Where can I get naloxone?

- There are some naloxone products that are designed for people to use in their home.
- Naloxone is available in pharmacies. Ask your healthcare provider about how you can get naloxone. In some states, you may not need a prescription.
- When you get your naloxone from the pharmacy, read the **Patient Information** on how to use naloxone and ask the pharmacist if anything is unclear.
- Tell your family about your naloxone and keep it in a place where you or your family can get to it in an emergency.

When you no longer need your opioid medicine, dispose of it as quickly as possible. The Food and Drug Administration recommends that most opioid medicines be promptly flushed down the toilet when no longer needed, unless a drug take-back option is immediately available. A list of the opioid medicines that can be flushed down the toilet is found here: https://www.fda.gov/drugdisposal

What things should I know about the specific opioid medicine that I am taking?

- Your healthcare provider has prescribed _____ for you. Read the Medication Guide for this medicine, which is information provided by your pharmacy.
- Remember this other important information about your opioid medicine:

Dosing instructions: _____

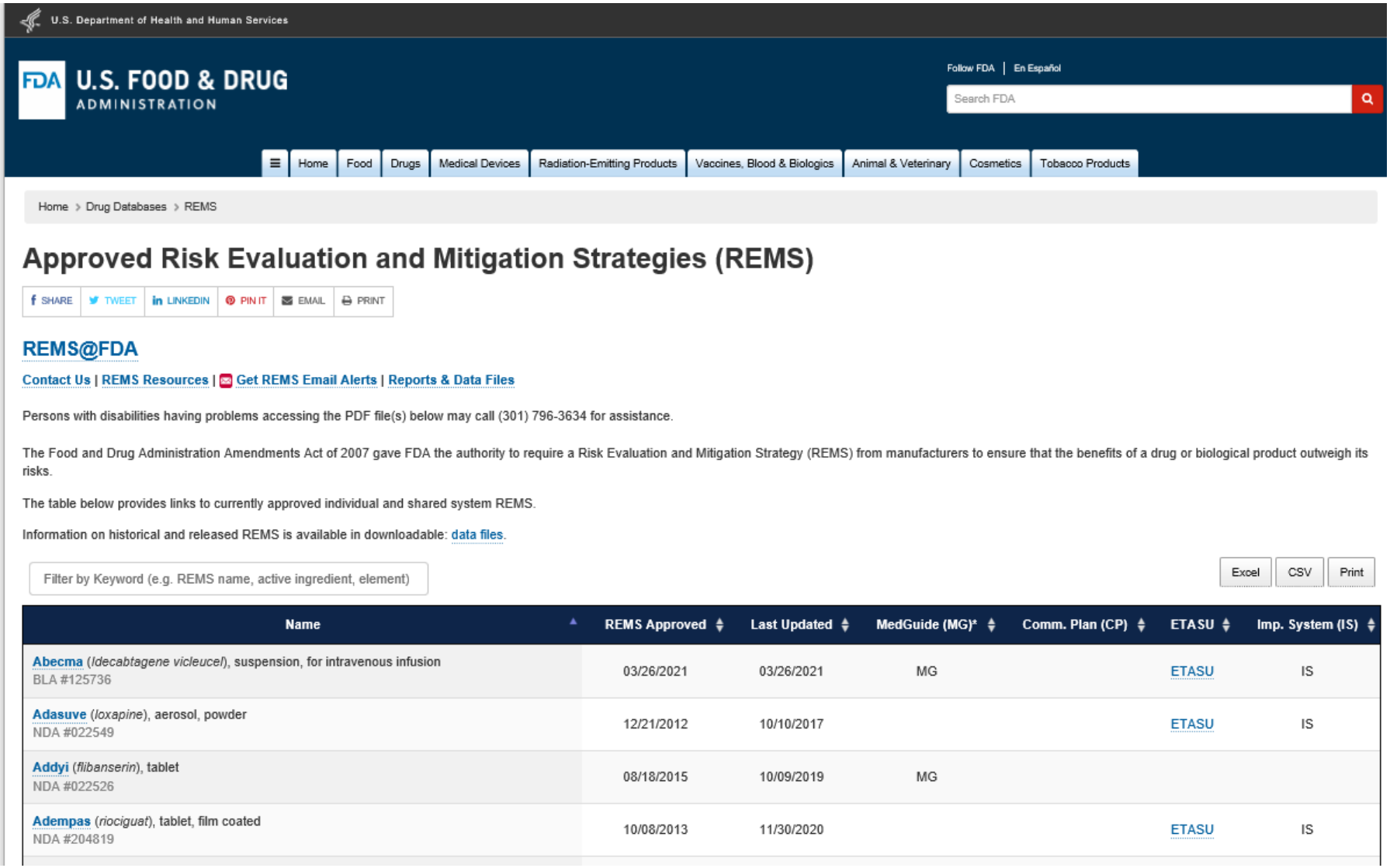
Any specific interactions with your medicines: _____

_____

What if I have more questions?

- Read the Medication Guide that comes with your opioid medicine prescription for more specific information about your medicine.
- Talk to your healthcare provider or pharmacist and ask them any questions you may have.
- Visit: www.fda.gov/opioids for more information about opioid medicines.

REMS@FDA



U.S. Department of Health and Human Services

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Approved Risk Evaluation and Mitigation Strategies (REMS)

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REMS@FDA

Contact Us | REMS Resources | Get REMS Email Alerts | Reports & Data Files

Persons with disabilities having problems accessing the PDF file(s) below may call (301) 796-3634 for assistance.

The Food and Drug Administration Amendments Act of 2007 gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks.

The table below provides links to currently approved individual and shared system REMS.

Information on historical and released REMS is available in downloadable: data files.

Filter by Keyword (e.g. REMS name, active ingredient, element)

Excel | CSV | Print

Name	REMS Approved	Last Updated	MedGuide (MG)*	Comm. Plan (CP)	ETASU	Imp. System (IS)
Abecma (*Idecabtagene vicleucel*), suspension, for intravenous infusion BLA #125736	03/26/2021	03/26/2021	MG		ETASU	IS
Adasuve (*loxapine*), aerosol, powder NDA #022549	12/21/2012	10/10/2017			ETASU	IS
Addyi (*flibanserin*), tablet NDA #022526	08/18/2015	10/09/2019	MG			
Adempas (*riociguat*), tablet, film coated NDA #204819	10/08/2013	11/30/2020			ETASU	IS

Adempas (riociguat) on REMS@FDA

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Home > Drug Databases > REMS

Approved Risk Evaluation and Mitigation Strategies (REMS)

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Adempas *(riociguat)*

NDA #204819

REMS last update: 11/30/2020

- View the Adempas Prescribing Information and Medication Guide at DailyMed.
- View Adempas's Regulatory Information at Drugs@FDA

Goals | Summary | REMS Materials | Update history

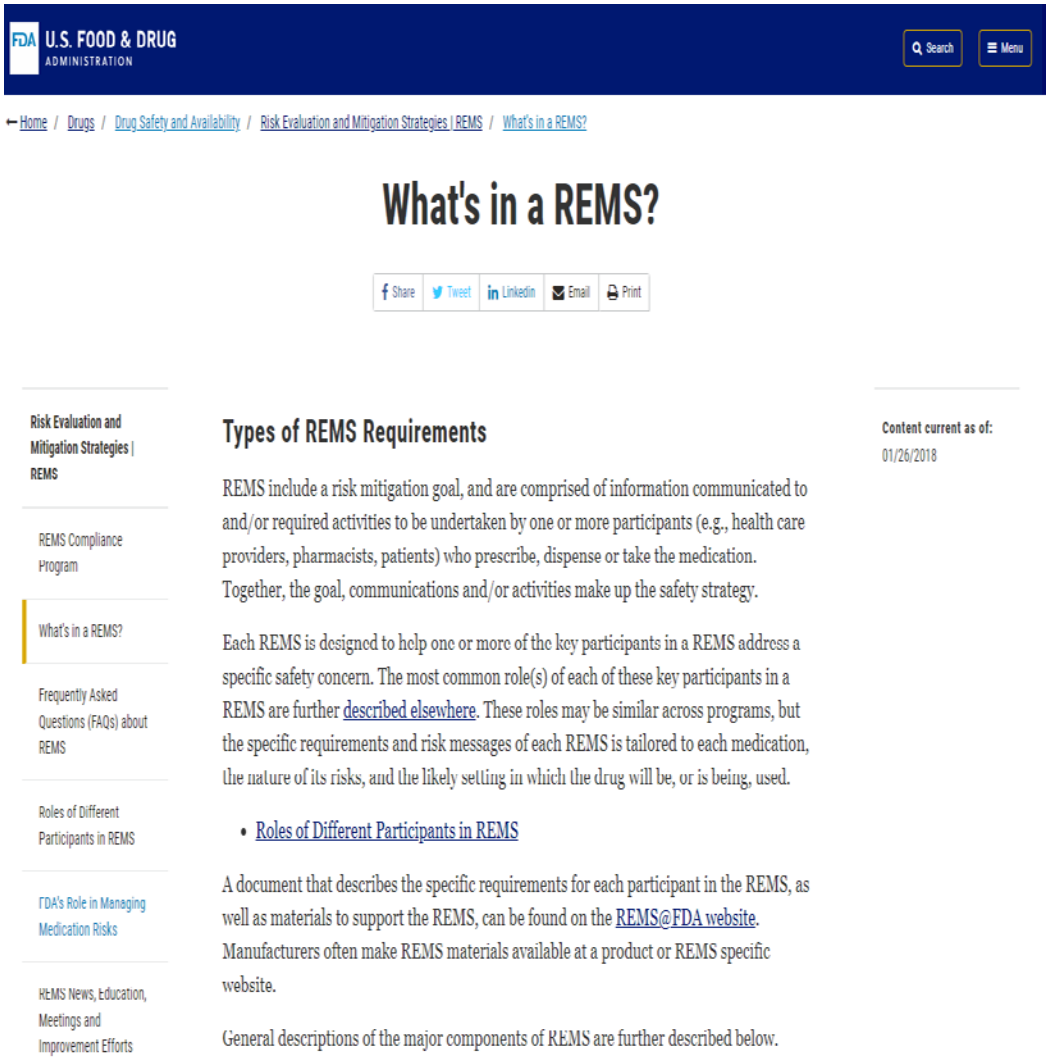
What is the purpose of the REMS?

The goal of the Adempas REMS Program is to mitigate the risk of embryo-fetal toxicity associated with Adempas by:

1. Ensuring prescribers are educated on the following:
   - the risk of embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
   - counseling patients about the risk and the need for monthly monitoring
   - enrolling patients in the Adempas REMS Program
   - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
   - the risk of embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
   - confirming that the appropriate patient monitoring and counseling has occurred before dispensing Adempas
5. Ensuring that patients are informed about:
   - the risk of embryo-fetal toxicity
   - appropriate baseline and monthly patient monitoring
   - appropriate contraception

Risk Evaluation and Mitigation Strategies (REMS) Resource Web Page

- Provides an overview of what is in a REMS
- Frequently asked questions and answers about REMS
- Roles of the different participants in a REMS
- REMS News, Education, Meetings and Improvement efforts



FDA Guidance on REMS

- **2011** Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)
- **2017** *Draft* - Format and Content of a REMS Document*
- **2017** *Draft* -Use of Drug Master File for Shared System REMS Submission
- **2017** *Draft* – Providing Regulatory Submissions in Electronic Format-Content of the REMS Strategies Document Using Structured Product Labeling
- **2018** *Draft* – Waivers of the Single, Shared System REMS Requirement
- **2018** *Draft* - Development of a Shared System REMS
- **2019** FDA's Application of Statutory Factors in Determining When a REMS is Necessary
- **2019** *Draft* - REMS Assessment: Planning and Reporting
- **2019** *Draft* - Survey Methodologies to Assess REMS Goals That Relate to Knowledge
- **2020** Risk Evaluation and Mitigation Strategies: Modifications and Revisions
- **2020** Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

* Revised the 2009 draft guidance for industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications*

Thank you!

Cynthia LaCivita, PharmD

Director, Division of Risk Management

FDA Drug Topics: Overview of Risk Evaluation and Mitigation Strategies (REMS) for Health Care Providers

Dipti Kalra, RPh, MS
Team Leader, REMS Compliance Team
Division of Enforcement and Postmarketing Safety
Office of Scientific Investigations, Office of Compliance
Center for Drug Evaluation and Research, US Food and Drug Administration

Outline

- Office of Compliance's Mission
- REMS Compliance Team Activities
- Possible Enforcement Actions
- REMS resources

Office of Compliance Mission

Mission: To shield patients from poor quality, unsafe, and ineffective drugs through compliance strategies and risk-based enforcement actions.

How we support the Mission

- Addressing patient health risks that arise from violations of FDA regulations and law
- Developing risk-based enforcement and communication strategies to reduce and prevent patient harm associated with these violations
- Ensuring drugs in FDA approval system have reliable evidence of safety and effectiveness and drugs meet postmarket safety requirements

https://www.fda.gov/about-fda/center-drug-evaluation-and-research/office-compliance

REMS Compliance Program Objectives

- Assess compliance with REMS requirements
- Verify accuracy of REMS assessment data submitted to the FDA
- Document implementation of the REMS

Office Collaboration

- Analyze REMS information to protect and promote public health
- Identify potential REMS compliance concerns

- Monitor industry compliance and conduct risk assessments
- Issue REMS inspections

- Conduct REMS inspections

REMS Compliance Team

Develops and implements compliance and enforcement programs by reviewing **Assessments** submitted by sponsors at specified times

Provides comments for **Modifications** to the REMS program

Assigns, directs and coordinates onsite **Inspections** in collaboration with Office of Regulatory Affairs in order to monitor adherence to statutes governing REMS requirements

Reviews **Establishment Inspection Reports** associated with REMS statutes, evaluates the evidence and possible risks to public health, and executes steps, such as regulatory actions, necessary to resolve compliance issues

Health Care Providers Collaboration in REMS

REMS Requirements for HCPs

Medication Guide

The Medication Guide should be available for distribution to patients at the time the patient is dispensed the drug

Communication Plan

Educates, informs, and raises awareness of risk: Dear Healthcare Provider (DHCP) letters, REMS letters, or letters addressed to HCPs through professional organizations, patient counseling tools for healthcare providers

Elements to Assure Safe Use (ETASU)

ETASU A: Certification or specialized training of HCPs who prescribe the drug
ETASU B: Certification of pharmacies, or other dispensers of the drug
ETASU C: Drug is dispensed to the patient only in certain health care settings
ETASU D: Drug is dispensed to patients with evidence of safe-use conditions
ETASU E: Each patient using the drug is subject to certain monitoring
ETASU F: Enrollment of treated patients in registries

Who do we Inspect?

- Sponsor/Application Holders
- Applicant's contractors

Applicant retains statutory obligation to ensure the REMS functions in accordance with the approved REMS

Site Selection Risk-based Considerations

- REMS with ETASU that has never been inspected
- REMS with ETASU with issues from previous inspection
- REMS with ETASU that was modified since last inspection
- REMS with communication plans that have never been inspected
- Input from other Offices

REMS Inspection Citations

Failure to comply with the **Medication Guide** distribution requirements

Failure to comply with REMS **Communication plan**

Failure to comply with **ETASU** requirements

Failure to comply with **Implementation plan**

REMS Inspection Classifications

NAI

No Action Indicated

- No objectionable conditions or practices were found during an inspection (or the objectionable conditions found, do not justify further regulatory action

VAI

Voluntary Action Indicated

- Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action

OAI

Official Action Indicated

- Regulatory and/or administrative actions will be recommended

REMS Compliance: Pandemic

FDA has issued guidance to communicate its temporary policy for certain risk evaluation and mitigation strategies (REMS) requirements for the duration of the public health emergency (PHE) declared by the Secretary of Health and Human Services (HHS) on January 31, 2020.

Guidance document available:

Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

https://www.fda.gov/media/136317/download

Legal Framework

Section 505-1 of the Food Drug and Cosmetic Act authorizes FDA to **require REMS**.

We enforce based on this statute. There are no regulations for REMS.

Possible Enforcement Action

- Warning Letters
- Seizure of the drug subject to the REMS
- Injunction
- Civil Monetary Penalties

Resources

FD&C Act Chapter V: Drugs and Devices

https://www.fda.gov/regulatory-information/federal-food-drug-and-cosmetic-act-fdc-act/fdc-act-chapter-v-drugs-and-devices

REMS@FDA Website

http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Risk Evaluation and Mitigation Strategies Compliance Program Manual

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-guidance-manual-cpgm/bioresearch-monitoring-program-bimo-compliance-programs

REMS Compliance Program

https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/rems-compliance-program

REMS Compliance Team email

CDER-OSI-REMS@fda.hhs.gov

1. Challenge Question

When can the FDA require a REMS?

a. REMS can be required preapproval if necessary to ensure the benefits outweigh the risks
b. REMS can only be required postapproval if packaging and safe disposal technologies for drugs are necessary to address the risk of abuse or overdose
c. REMS can be required post-approval if FDA becomes aware of new safety information
d. REMS can be required preapproval if necessary to ensure the benefits outweigh the risks or post-approval if FDA becomes aware of new safety information

2. Challenge Question

Which can be an element of a REMS?

a. Prescribers have specific training/experience or special certifications

b. Drug be dispensed only in certain healthcare settings (e.g., infusion settings, hospitals)

c. Drug be dispensed with evidence of safe-use conditions such as laboratory tests

d. All of the above

3. Challenge Question

Which FDA resource on REMS provides a complete listing of the active REMS?

a. DRUGS@FDA

b. Risk Evaluation and Mitigation Strategies (REMS) Resource Web Page

c. REMS@FDA

d. FDA's Application of Statutory Factors in Determining When a REMS is Necessary

4. Challenge Question

Which of the following is <u>not</u> a REMS citation?

a. Failure to comply with REMS Medication Guide
b. Failure to comply with REMS Financial Records
c. Failure to comply with REMS Communication Plan
d. Failure to comply with REMS Elements to Assure Safe Use (ETASU)