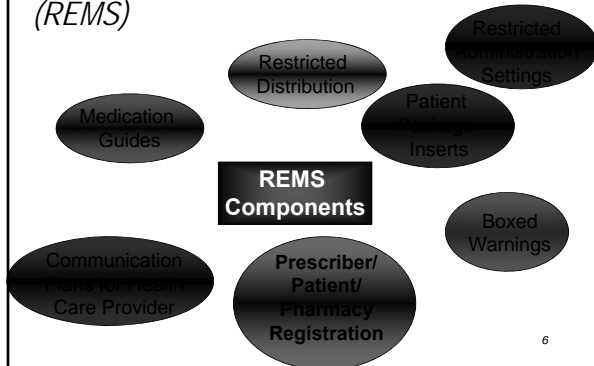


Food and Drug Administration Amendments Act (FDAAA) of 2007

- Significant increase in FDA authority
- Granted resources needed to conduct comprehensive reviews for new drugs and devices
 - ◆ Proposed \$4 Billion Budget
- More research and development of treatments for children
- Applicants for new drugs and biologicals must submit Risk Evaluation and Mitigation Strategies (REMS) if the FDA determines there must be a mechanism to assure benefit out weighs risks

5

Risk Evaluation and Mitigation Strategies (REMS)



6

Example: REMS for Opioids

- Announced by FDA February 10, 2010

Fentanyl	Hydromorphone	Methadone
Morphine	Oxycodone	Oxymorphone

- Risks when used improperly
- Misuse, abuse, and overdoses continue to increase
- 5.2 million persons age 12 or older use prescription opioids recreationally per month

7

2009 -2010 Medication Guides

In June, 2009, the FDA released over 100 new medication Guides including SSRI, SSNRI and Tricyclic antidepressants, all NSAIDS, fluoroquinolones, newer anticonvulsants, rosiglitazone, and atypical antipsychotics.

Abilify	Botox	Coumadin	Forteo
Actiq	Byetta	Darvocet Darvon	Kaletra
Actos	Celexa	Daytrana	Keppra
Ampyra	Cellcept	Edludar	Lamictal/ Lamictal XR
Androgel	Cordarone	Effient	Morphine Sulfate Oral Solution

2009 -2010 Medication Guides

Lyrica	Pennsaid	Remicade	Topamax
Metosolv ODT	Pristiq	Savella	Victoza
Multaq	Prozac	Seroquel Seroquel XR	Videx/ Videx EC
Myfortic	Qaliquin	Symbicort	Voltaren
Onsolis	Reglan	Symbyax	Wellbutrin, SR, XL
Zenpep	Zonergan	Zyban	Zyprexa

Recent Labeling Changes

CYP2C19: genetic variations and drug interactions reduce activity. Concomitant use of H2 Blockers

PLAVIX®

Risk of hemolytic anemia in genetic G6PD deficiency

Sulfonylureas

Substitution of other fentanyl products may result in fatal overdose; do not convert to other fentanyl products on a mcg to mcg dose.

ACTIQ®

Recent Labeling Changes

Warnings for Hyperglycemia, hyperlipidemia, weight gain, increase in lipids, increased triglycerides, leukopenia/neutropenia

Antipsychotics
Class effect

Warnings for acute pancreatitis, Hemorrhagic, necrotizing pancreatitis, hypersensitivity reactions, patient counseling

Januvia®
Sitagliptin
combinations

Warning: Hypersensitivity, urinary retention

Spiriva®

11

Recent Labeling Changes

Contraindication: abnormality of the esophagus, irritation, follow w/6-8 oz H2O

Bisphosphonate
Class effect

Box warning; epidural/spinal hematoma with Neuraxial anesthesia or spinal puncture, neuro monitoring

LMWHs
Heparinoids

ADRs: Memory impairment; QT interval impairment

Oxybutynin

12

Recent Labeling Changes

Med Guide: Risk of Tardive Dyskinesia

Metoclopramide

Risk of overdose and cardiovascular Events, life-threatening arrhythmias

Darvon®,
Darvon-N®
Darvocet-N®

Med Guide: Reports of Congestive Heart Failure: significant public health threat

Actos®

13

Recent Labeling Changes

Med Guide: Pleural effusion,
demyelinating polyneuropathy

Warnings: Acute pancreatitis, should not
Reports of acute renal failure and insufficiency

Medication Guides & Physician Registry:
ESAs may cause tumors to Grow in CA patients,
death, develop clots, heart attack, heart failure,
stroke

Amiodarone

Byetta®

Aranesp®
Epogen®
Procrit®

Recent Labeling Changes

Warnings: Hepatic Effects: elevated
Transaminases, hepatotoxicity, use
lowest dose, shortest duration

Warnings: Serotonin Syndrome; Seizures/
serotonin syndrome with SSRI, SSNRI, Triptans

Voltaren Gel®

Tramadol
Tramadol/APAP

15

*Important Drugs Approved by the FDA –
2009 to Present*

16

Morphine Sulfate Oral Solution

- Old drug, new FDA approval January 25, 2010
 - ◆ FDA unapproved drugs initiative to assure marketed drugs meet FDA standards
 - ◆ Assures manufacturers provide information to safely prescribe and use medications

Approved for moderate to severe acute and chronic pain
 Available 100 mg/5 mg (20 mg/ml)
 This is the only approved concentration

17

*Olepto[®], Labopharm
 Trazodone Extended Release*

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ● 150 mg, 300mg ● "Bisectable" tablets ● Do not crush ● Take HS preferably ● On empty stomach 	Major Depressive Disorder	<ul style="list-style-type: none"> ● 75 mg PO daily ● Increase by 75 mg daily every 3 days, maximum dose = 375 mg 	<ul style="list-style-type: none"> ● Box Warning ● Suicidal thinking and behavior in children, adolescents, young adults ● Med Guide

18

*Monitoring Olepto[®], Labopharm
 Trazodone Extended Release*

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●Somnolence ●Headache ●Dry Mouth ●Nausea ●Fatigue 	<ul style="list-style-type: none"> ●MAOIs, CNS Depressants ●CP450 inhibitors/ inducers ●Digoxin ●Phenytoin ●Serotonergics ●NSAIDs, ASA ●Warfarin

19

Xiaflex® (collagenase clostridium histolyticum, Auxilium, Inc.)

Description	Indication	Dose	ADRs
<ul style="list-style-type: none"> ● Biologic injectable ● Replaces surgery; injected into the collagen cord of the hand 	Dupuytren's Contracture	<ul style="list-style-type: none"> ● To be injected by a health professional experienced with hand injections 	<ul style="list-style-type: none"> ● Edema ● Swelling ● Bleeding ● Pain at injection site

20

Milnacipran (Savella®, Forest)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ● SSNRI ● Tablets, 12.5mg, 25 mg, 50 mg, 100 mg ● Take with or without food ● Food may improve tolerability ● Titration pack 	● Fibromyalgia	<ul style="list-style-type: none"> ● 50 mg PO twice a day ● Titrate 12.5 mg on day one, 12.5mg on days two & three, 25 mg BID on days four through seven, 50 mg BID thereafter ● Adjust for renal impairment 	<ul style="list-style-type: none"> ● Box Warning ● Suicidal thinking and behavior in children, adolescents, young adults ● Med Guide ● Produces physical dependence

Monitoring Milnacipran (Savella®, Forest)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ● Nausea ● Constipation ● Hot Flush ● Hyperhidrosis(sweating) ● Vomiting ● Increased heart rate ● Dry Mouth ● Hypertension 	<ul style="list-style-type: none"> ● Lithium ● Epinephrine/norepinephrine ● Digoxin ● Clonidine ● Clomipramine ● MAOs ● Serotonergics

22

Saxagliptin (Onglyza® , BMS)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ●Dipeptidyl peptidase inhibitor, slows inactivation of incretin hormones ●Tablets, 2.5 mg, 5 mg ● Take with or without food 	<ul style="list-style-type: none"> ●Adjunct to diet and exercise to improve Type 2 Diabetes 	<ul style="list-style-type: none"> ● 2.5 mg or 5 mg PO daily ● 2.5 mg PO daily for patients with renal impairment ●Assess renal function before initiation 	<ul style="list-style-type: none"> ● N/A

23

Monitoring Saxagliptin (Onglyza® , BMS)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●UTI ●URI ●Headache ●Hypoglycemia ●Swelling & fluid retention (may be worse with thiazolidinediones) ●Hypersensitivities <ul style="list-style-type: none"> ◆Rash, hives, swelling of face, throat, lips 	<ul style="list-style-type: none"> ●Rifampin ●Diltiazem (increased) ●Ketoconazole (increased)

24

Dronedarone (Multaq, Sanofi-Aventis)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ●Anti-arrhythmic ●Tablets, 400 mg film-coated ●No grape-fruit juice ●>2000 Geriatric pts in studies 	<ul style="list-style-type: none"> ●Reduce risk of CV hospitalization in paroxysmal or persistent A-Fib, A-Flutter with recent episodes & CV risk factors, >70 yo 	<ul style="list-style-type: none"> ●400 mg two times a day with AM & PM meal ●Tx with Class I or II antiarrhythmics and strong inhibitors CYP3A (ketoconazole) must be stopped before initiation 	<ul style="list-style-type: none"> ●Box warning ●Contraindicated in Class IV HF, Class II-III HF requiring hospitalization ●Two-fold mortality rate in severe HF

25

Monitoring Dronedaronone (Multaq, Sanofi-Aventis)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●Diarrhea ●Vomiting ●Abdominal pain ●Nausea ●Asthenia 	<ul style="list-style-type: none"> ●Antiarrhythmics ●Calcium Channel Blockers ●Beta Blockers ●Digoxin ●HMG-CoAs ●Tacrolimus, Sirolimus

26

Rufinamide (Banze®/Esai)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ●Anti-epileptic ●Tablets, 200, 400 mg film-coated, scored ●May be crushed ●Give with food 	<ul style="list-style-type: none"> ●Adjunctive tx of seizures associate with Lennox – Gastout syndrome in children 4 years to adults 	<ul style="list-style-type: none"> ●Adults 400 – 800 mg twice a day. Increase 400 – 800 mg every 2 days to a max. of 3200 mg ●Children: 10 mg/kg/day in 2 equally divided doses. Increase by 10 mg/kg/day to 45 mg/kg/day 	<ul style="list-style-type: none"> ●Medication Guide ●Gradual withdrawal

27

Monitoring Rufinamide (Banze®/ Eisai)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●Suicidal behavior and ideation ●Somnolence/fatigue ●Coordination abnormalities, gait disturbance, ataxia, (ADLs), dizziness ●QT shortening ●Asthenia ●Headache 	<ul style="list-style-type: none"> ●Phenytoin ●Valproate ●Carbamazepine ●Phenobarbital ●Primidone ●Triazolam

28

Prasugrel (Effient® Lilly)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ●Anti-platelet therapy ●Tablets, 5 mg and 10 mg non-scored ●Give with or without food ●Head to head with clopidogrel ●Action is rapid, irreversible for life of platelet 	<ul style="list-style-type: none"> ●Acute Coronary Syndrome to reduce the rate of thrombotic cardiovascular events, including stent thrombosis 	<ul style="list-style-type: none"> ●Initiate with 60 mg loading dose. Continue with 10 mg daily. ●5 mg daily for patients < 60 KG ●Should be taken with aspirin 	<ul style="list-style-type: none"> ●Medication Guide ●Box Warning ●Contra-indicated in pts with prior TIA or stroke

29

Prasugrel (Effient® Lilly)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●Increased risk of bleeding – increases with age ●Thrombocytopenic Purpura ●Angioedema ●Anemia ●Thrombocytopenia ●Abnormal hepatic fcn ●Angioedema 	<ul style="list-style-type: none"> ●Warfarin ●NSAIDs <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> Can be given with aspirin, heparin, statins, digoxin, PPIs, H2 Blockers </div>

30

Bromocriptine Mesylate, Cycloset®, (VeroScience)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ●Dopamine receptor agonist ●Tablets, 0.8 mg ●Taken within 2 hours after waking in AM ●Give with food ●Reduces insulin resistance 	<ul style="list-style-type: none"> ●Adjunct to diet and exercise to improve glycemic control in adults with Type 2 DM ●Not for use in Type 1 DM 	<ul style="list-style-type: none"> ● Initiate with 0.8 mg daily, increased by 1 tablet weekly until an maximal tolerated dose of 1.6 to 4.8 mg is achieved 	

31

Monitoring Bromocriptine Mesylate, Cycloset® (VeroScience)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●Hypotension (Monitor BP before initiating and during therapy) ●Syncope ●Psychosis ●May reduce efficacy of drugs that treat psychosis ●Somnolence ●Nausea 	<ul style="list-style-type: none"> ●Olanzapine, Clozapine, Ziprasidone ●May increase unbound fraction of protein-bound therapies ●Metoclopramide ●Ergot-related drugs ●Metabolized by CYP3A4 ●Hypotension and tachycardia with sympathomimetic drugs

Febuxostat (Uloric®, Takeda)

Description	Indication	Dose	REMS
<ul style="list-style-type: none"> ●Xanthine oxidase inhibitor ●Tablets, 40 mg, 80 mg ●Take with or without food, no regard for antacids 	<ul style="list-style-type: none"> ●Chronic management if hyperuricemia in patients with gout. ●Not recommended for asymptomatic hyperuricemia 	<ul style="list-style-type: none"> ● Initiate with 40 mg daily. ●Increase dose to 80 mg for patients who do not achieve a serum uric acid < 6 mg/dL after 2 weeks ●No dose adjustment with hepatic/renal impairment, age 	<ul style="list-style-type: none"> ●Medication Guide

Febuxostat (Uloric®, Takeda)

Adverse Events	Drug Interactions
<ul style="list-style-type: none"> ●Arthralgia ●Liver function abnormalities ●Nausea ●Rash ●Gout flare ●MI, stroke > allopurinol ●LFTs periodically recommended 	<ul style="list-style-type: none"> ●Azathioprine ●Mercaptopurine ●Theophylline

New Injections

Actemra® (tocilizumab, Genentec): Moderate to severe rheumatoid arthritis

Zyprexa Relprevv® Extended release injection (olanzapine, Lilly): Schizophrenia

Istodax® (Romidepsin, Gloucester): cutaneous T-Cell lymphoma

Stalera® (Ustekinumab, Centocor Ortho Biotech): Moderate to severe plaque psoriasis

Abilify® (Aripiperazole, Otsuka) IM use only

35

New OTCs and Topicals

Zegerid OTC® (Omeprazole and Sodium Bicarbonate, Merck): Heartburn

Qutenza® Transdermal Patch (Capsaicin, NeurogesX): Postherpetic neuralgia

Pennsaid Topical Solution® (Diclofenac, Nuvo): Osteoarthritis of the knee

Zirgan® (ganciclovir ophthalmic gel, Sirion): Herpetic keratitis

36

New Me, too! drugs

The U.S. FDA has approved a name change for Kapidex to avoid confusion w/Casodex and Kadian. Effective in late April 2010, Takeda will market Kapidex under the new name **Dexilant**

Follow-on Drug	Innovator Drug
Armodafinil (Nuvigil®)	Provigil®
Dexlanoprazole (Kapidex®)	Prevacid®
Desvenlafaxine (Pristiq®)	Effexor®
Fenofibric acid (Trilipix®)	Tricor®
Fesoterodine (Toviaz®)	Detrol LA®
Pitavastatin (Livalo®)	Zocor®

37

Old Drugs, new dosage forms

Actoplus Met XR®	Metformin/pioglitazone
Astepro®	Azelastine
Caldolor	Injectable ibuprofen
Eludar®	Sublingual zolpidem
Gelnique	Topical gel oxybutinin
Invega Sustenna	Monthly injectable paliperidone ³⁸

Old Drugs, New Dosage Forms

Lamictal ODT®, Lamictal XR	Lamotrigine
Lipsovir® Ointment	Acyclovir/hydrocortisone
Metozolv ODT®	Metocopramide
Onsolis®	Fentanyl buccal
Revatio®	Sildenafil injection
Twynstra®	Telmisartin/amlodipine

New Indications for Existing Drugs

- **Rosuvastatin (Crestor®, AZ)**
- Primary PREVENTION of cardiovascular disease to reduce the risk of stroke, heart attack, and risk of arterial revascularization procedures **in individuals who have NO evident heart disease**
 - ◆ Age (men>50 years, women> 60 years)
 - ◆ **Elevated high-sensitivity C-reactive protein (hsCRP) ≥2 mg/L**
 - ◆ One additional cardiovascular risk factor (high blood pressure, family hx of premature heart dx, low LDL, ⁴⁰ smoking)

How was the decision made?

- **Justification** for the use of statins in Prevention: an Intervention Trial Evaluation Rosuvastatin
- Compared Crestor 20 mg to placebo in the time to first occurrence of cardiovascular deaths.
 - ◆ 18,000 individuals
 - ◆ 44% risk reduction
- Not for use in patients with elevated hsCRP alone

41

New Indications for Existing Drugs

- **Tiotropium (Spiriva®, B-I)**
- Approved for daily use in COPD
- Studies performed in 26 VA Medical Centers
- Lengthens interval between exacerbations by 4 months
 - ◆ Decreased number of exacerbation days
 - ◆ Decreased incidence of hospitalization
- Not likely to increase cardiovascular risk
- Remember: *TWO inhalations per capsule*

42

Antipsychotics

- | |
|---|
| Abilify: approved for autism in children |
| Zyprexa: Approved for bipolar and schizophrenia in adolescents |
| Seroquel: Approved for bipolar and schizophrenia in adolescents, major depressive disorder, generalized anxiety disorder |
| Symbiax: Depressive episodes associated with bipolar I Disorder, treatment resistant depression |

43

First Time Generics - 2009

Donepezil ODT, Aricept ODT	Ketorolac Ophth, Acular LS, Soln	Lansoprazole, Prevacid	Peridopril, Aceon
Polyethylene glycol, Miralax	Fentanyl Transmucosal, Actiq	Nateglinide, Starlix	Piperacillin/ Tazobactam, Zosyn
Tacrolimus, Prograf	Clonidine Transdermal, Catapres TTS	Levonorgestrel, Plan B	Bicalutamide, Casodex
Triamcinolone Nasal Spray, Nasacort	Omeprazole OTC, Prilosec OTC	Oxcarbazepine oral susp, Trileptal Susp	Topiramate, Topamax
Lorazepam oral Conc, Intensol	Azelastine Nasal Soln, Astelin	Risperidone ODT, Risperdal M	

Anticipated Generics Coming in 2010

- Cozaar®/Hyzaar® (Merck)
- Effexor XR® (Pfizer)
- Flomax® (BI)
- Ambien CR® (Sanofi-Aventis)
- Astelin® (Meda)

45

2010 Pipeline

- FDA is working to get older NDA's approved
- FDA focus: Drugs that treat Type 2 Diabetes and safety in drugs used to treat cardiovascular disorders (oral heparanoids)
- We'll see more head to head studies

46

On the Horizon
Multiple Sclerosis

- Multiple Sclerosis is a development area in 2010
- Oral products
- Goal: Avoiding relapse
- **Fingolimod**, (Novartis)
- **Fampridine** (Amaya, Acorda)
- **Cladibrine** (EMD Serono/Merck)

47

*The Diabetes Battleground**

- New data submitted to the FDA requires studies that demonstrate no increase in cardiovascular (CV) risk
- **Liraglutide** (Victoza, Novo)
 - ◆ Glucagon-like peptide analogue and a long acting, once weekly injection
- **Exenatide LAR** (Byetta, Lilly)
 - ◆ long acting, once weekly injection
- **Inhaled Insulin** (Afresa, MannKind)
 - ◆ Rapid acting meal-time insulin
- **Teplizumab** (Lilly/Macrogenics)
 - ◆ Type 1 Diabetes
- **Dapaglifozin** (BMS/AZ)
 - ◆ Increases urinary glucose excretion

48

Pain Management

- **Duloxetine** (Cymbalta, Lilly)
 - ◆ NDA submitted to treat chronic pain
- **Naproxen** (NicOx)
 - ◆ NSAID, cyclo-oxygenase inhibiting oxide donor for osteoarthritis, fewer cardiovascular and GI side effects, favorable blood pressure effect
- **Naproxen/esomeprazole** (Vimovo, AZ/POZEN)
 - ◆ OA, RA, ankylosing spondylitis in patients with risk of gastric ulcers

49

Cardiovascular (CV) Disease

- Oral Anticoagulants
 - ◆ Rivaroxaban (Bayer/J&J): oral LMWH
 - ◆ Dabigatran (
- Other CV drugs
 - ◆ Rosuvastatin/fenofibric acid

50

*Knowledge is of two kinds.
We know a subject ourselves,
or we know
where we can find information on it.*

Samuel Johnson, quoted in *Boswell's Life of Johnson*
English author, critic, & lexicographer (1709 - 1784)

51

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53

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54
