New Drug Update 2011

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Objectives

• Review a selection of medications approved by the Food and Drug Administration (FDA) in 2011
• Discuss FDA market withdrawals and other safety alerts that affect patient care
• Identify resources that can be used to stay up-to-date with actions by the FDA

New Drug Entity Approvals

• Information is reported by the FDA

• FDA Review Process
  – Regular review
  – Expedited review
    • Orphan disease
    • Fast track designation
    • Accelerated approval program
    • Priority review

Abbreviations

• ACS – acute coronary syndrome
• ADR – adverse drug reaction
• AF – atrial fibrillation
• BP – blood pressure
• BMS – bone marrow suppression
• BW – U.S. Boxed Warning
• CV – cardiovascular disease
• CR – complete response
• DVT – deep vein thrombosis
• D – diarrhea
• GI – gastrointestinal
• HR – hazard ratio
• N – nausea
• NSAIDs – non-steroidal anti-inflammatory drugs
• PR – partial response
• PAP – patient assistant program
• PE – pulmonary embolism
• SJS – Stevens-Johnson syndrome
• SVR – systemic virologic response
• VTE – venous thromboembolism
• V – vomiting

NEW APPROVALS

CARDIOVASCULAR

Complete list at CenterWatch: http://www.centerwatch.com/drug-information/fda-approvals/
Azilsartan kamedoxomil (Edarbi™)

- Angiotensin receptor blocker (ARB)
- Literature
  - Reductions in BP
    - -14.3 vs -10 vs -11.7 mmHg
- Warnings and ADRs
  - Pregnancy [BW], hypovolemia
  - Similar to other ARBs
- Drug Interactions
  - NSAIDs
- Dose
  - 80 mg PO daily; dose adjust in volume depletion

Dabigatran etexilate (Pradaxa®)

- Prevention of stroke
- Literature
  - RE-LY (MC, MN, R, parallel group) compared with warfarin
    - HR 0.65 (0.52 - 0.81) P = 0.0002
- Warnings and ADRs
  - Bleeding; FDA safety alert in December 2011
  - No reversal guidelines
- Drug Interactions
  - P-glycoprotein inducers, dronedarone, ketoconazole, clopidogrel, St. John’s wort
  - Medications that affect bleeding
- Dose
  - 150 mg PO twice daily; renal adjustments

Ticagrelor (Brilinta™)

- Reduction of thrombotic events ACS
- Literature
  - PLATO: compared with clopidogrel
    - Efficacy: 9.8% vs 11.7%
    - Safety: 11.6% vs 11.2% [major bleeding]
- Warnings and ADRs
  - Bleeding [BW], dyspnea
- Drug Interactions
  - CYP3A4 inhibitors and inducers, digoxin, simvastatin/lovastatin
  - Medications that affect bleeding
- Dose
  - 180 mg PO loading dose; 90 mg PO twice daily
  - Aspirin therapy

Rivaroxaban (Xarelto®)

- Indications
  - Reduction of stroke and systemic embolism from AF
  - Prophylaxis of DVT during knee or hip replacement
- Literature
  - RECORD 1, 2, 3; ROCKET; EINSTEIN
    - Total VTE: RRR – 48% to 76%
  - AF: noninferior to warfarin
- Warnings and ADRs
  - Spinal/epidural hematoma [BW]
  - Bleeding
- Drug Interactions
  - CYP3A4 inhibitors and inducers; medications that affect bleeding
- Dose
  - 10 mg or 20 mg PO daily

Quick Stop Question 1

- After obtaining a medical history for a newly admitted patient, you notice on the H&P that the patient is pregnant.
  - PMH: hypertension, 8 weeks pregnant, constipation
  - Medications: prenatal vitamin, azilsartan, docusate
- What recommendation do you have for the medical team?
Quick Stop Question 2

• New admitted patient is undergoing total hip replacement. The medical team has a concern about the use of warfarin in this patient.
• What new anticoagulant could be used to reduce the risk of DVT?

Crizotinib (Xalkori®)

• Advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase +
• Literature
  – 3 CRs and 136 PRs for 50% response rate
  – Response duration = 40-48 weeks
• Warnings and ADRs
  – Pneumonitis, hepatic effects, QT prolongation
  – Vision disorder, N, V, D, edema, constipation, increased ALT, neutropenia
• Drug Interactions
  – CPY3A4 inhibitors/inducers, drugs that prolong the QT interval, drugs that elevate the gastric pH, grapefruit
• Dose
  – 250 mg PO twice daily; dose adjustments for hematologic toxicities

Ipilimumab (Yervoy™)

• Unresectable or metastatic melanoma
• Literature
  – Survival at 1 year – 46% vs 25%
  – Median overall survival = 10 months
• Warnings and ADRs
  – Immune-mediated reactions [BW]
  – Fatigue, diarrhea, pruritus, rash, colitis
• Drug Interactions
  – Potential: digoxin, warfarin
• Dose
  – 3 mg/kg IV (over 90 min) every 3 weeks for 4 doses
  • Must dilute and use an in-line filter
  • Adjust schedule/dose for toxicities

Vemurafenib (Zelboraf™)

• Unresectable or metastatic melanoma with BRAF** mutation
• Literature
  – Treatment naïve: overall response – 48% vs 5%
  – Median survival – 11 months vs 1.6 months
  – Prior therapy: overall response – 52%
• Warnings and ADRs
  – Cutaneous squamous cell carcinoma, dermatologic reactions, QT prolongation, liver abnormalities, ophthalmic effects
  – Edema, alopecia, arrhythmias, fatigue, N, photosensitivity, rash
• Drug Interactions
  – CYP3A4 and P-glycoprotein inhibitors/inducers, drugs that prolong the QT interval, warfarin
• Dose and Administration
  – 960 mg PO twice daily; dose adjustments for toxicities
  • Swallow with full glass of water; do not crush or chew
### Abiraterone acetate (Zytiga™)
- Metastatic, castration-resistant prostate cancer
- Literature
  - Mean overall survival: 14.8 m vs 10.9 m
  - Trial terminated early
- Warnings and ADRs
  - Pregnancy, hepatotoxicity, CV disease
  - Edema, triglycerides, electrolytes, diarrhea, LFTs, hyper tension, hot flush
- Drug Interactions
  - CYP3A4 and P-glycoprotein inhibitors/inducers
- Dose
  - 1000 mg PO daily (prednisone 5 mg PO twice daily)
  - Dose adjustments in hepatic impairment

### Brentuximab vedotin (Adcetris™)
- Refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL)
- Literature
  - HL: overall response rate – 73%
  - sALCL: overall response rate – 86%
- Warnings and ADRs
  - Progressive multifocal leukoencephalopathy (PML)[BW]
  - Bone marrow suppression, peripheral neuropathy, SJS
- Drug Interactions
  - Bleomycin (contraindicated)
- Dose
  - 1.8 mg/kg IV every 3 weeks [maximum: 180 mg]
  - Administer over 30 minutes; do not push
  - Dose adjustments for toxicities

### Vandetanib (Caprelsa®)
- Metastatic, advanced thyroid cancer
- Literature
  - Progression-free survival: HR = 0.35 [0.24-0.53]
  - Overall response rate: 44% vs 1%
- Warnings and ADRs
  - QT prolongation [BW]
  - N, D, rash, acne, hypertension, pulmonary toxicity
- Drug Interactions
  - CYP3A4 inhibitors/inducers, drugs that prolong the QT interval, St. John’s wort
- Dose
  - 300 mg PO daily
  - Dose adjustment in renal impairment and QT prolongation

### Eribulin mesylate (Halaven™)
- Late stage metastatic breast cancer
- Literature
  - Increased survival: 2.5 months
- Warnings and ADRs
  - BMs, peripheral neuropathy, QT prolongation
  - Fatigue, alopecia, N, D, constipation, increased ALT
- Drug Interactions
  - Drugs that prolong the QT interval
- Dose
  - 1.4 mg/m²/dose IV, days 1 and 8 [21-day cycle]
  - Infuse over 2 to 5 min (diluted or undiluted)

### Deferiprone (Ferriprox®)
- Chelating agent – treatment of transfusional iron overload
- Literature
  - ≥ 20% decline in serum ferritin: 50% [43%-27%]
- Warnings and ADRs
  - Agranulocytosis [BW], hepatotoxicity, QT prolongation
  - N, V, abdominal pain, chromaturia, headache, arthralgia
- Drug Interactions
  - Mineral supplements, antacids with polyvalent cations
- Dose
  - 25 to 33 mg/kg PO three times daily
  - Round to nearest 250 mg; maximum – 99 mg/kg/day
  - Interrupt therapy for ANC < 1500/mmk

### Quick Stop Question 3
- Like many of the medications approved for cancer, vandetanib help address an unmet medical need for advanced thyroid cancer.
- What type of FDA expedited review did vandetanib receive?
Quick Stop Question 3

Fidaxomicin (Dificid™)
- Treatment of Clostridium difficile-associated diarrhea
  - Bactericidal; MIC range 0.03 – 0.25 mcg/mL
- Literature
  - Non-inferior to oral vancomycin
    - Clinical response: 88% vs 86%/87%
    - Sustained clinical response: 70%/72% vs 57%
- Warnings and ADRs
  - Not for treatment of systemic infections
  - N, V, abdominal pain, GI hemorrhage, anemia, neutropenia
- Drug Interactions
  - None reported
- Dose
  - 200 mg PO twice daily [10 days]
  - No adjustments needed for renal or hepatic impairment

Boceprevir (Victrelis™)
- Treatment of chronic hepatitis C
- Literature
  - SPRINT-2: SVR – 66% vs 63% vs 38%
  - RESPOND-2: SVR – 66% vs 59% vs 21%
- Warnings and ADRs
  - Substrates/inducers of CYP3A4, serious skin reactions
    - Fatigue, anemia, N, headache, dysgeusia
- Drug Interactions
  - CYP3A4 substrates/inducers, warfarin, digoxin, colchicine
  - Ritonavir-boosted HIV protease inhibitor regimens
- Dose
  - 800 mg PO three times daily [with food]
  - Peginterferon alfa and ribavirin
  - Response-guided therapy based on HCV-RNA results

Telaprevir (Incivek™)
- Treatment of genotype 1 chronic hepatitis C
- Literature
  - Overall SVR = 74% vs 46%
  - On-treatment virologic failure = 7% vs 29%
- Warnings and ADRs
  - Substrates/inducers of CYP3A4
    - Pruritis, anemia, N, V, D, hemorrhoids, dysgeusia
- Drug Interactions
  - CYP3A4 substrates/inducers, warfarin, digoxin, colchicine
- Dose
  - 750 mg PO three times daily [with food]
  - Peginterferon alfa and ribavirin
  - Response-guided therapy based on HCV-RNA results

Rilpivirine (Edurant™)
- Treatment of HIV
- Literature
  - Non-inferior to efavirenz in combination with fixed regimen
    - Undetectable viral load: 84.3% vs 82.3%
- Warnings and ADRs
  - CYP3A4 inducers, drugs that increase gastric pH, depressive disorders, fat redistribution, immune reconstitution syndrome
    - Insomnia, headache, rash, liver enzyme changes
- Drug Interactions
  - CYP3A enzyme inhibitors, drugs that prolong the QT interval, proton pump inhibitors
- Dose
  - 25 mg PO daily [with a meal]
Belimumab (Benlysta®)

- Systemic lupus erythematosus
  - Autoantibody-positive [ANA and/or anti-ds-DNA]
- Literature
  - SLE Responder Index
    - Trial 2: 34% vs 41% vs 43%
    - Trial 3: 44% vs 51% vs 58%
- Warnings and ADRs
  - Infusion reaction, serious infections, malignancy, psychiatric effects, live immunizations
  - N, D, pyrexia, insomnia, pain in extremity, depression, migraine
- Drug Interactions
  - Live immunizations, others not well documented
- Dose
  - 10 mg/kg IV at 2-week intervals [3 doses]; then 4-week intervals
  - *Infuse over 1 hour

Roflumilast (Daliresp®)

- Chronic obstructive pulmonary disease
- Literature
  - Reduction in rate of exacerbations (15%, 18%)
  - Only significant in severe COPD with associated chronic bronchitis or exacerbations in the previous year
- Warnings and ADRs
  - Moderate-to-severe liver impairment, CNS, weight loss
  - N, D, weight decrease, headache, back pain, insomnia, dizziness, decreased appetite
- Drug Interactions
  - Strong CYP3A4 inducers/inhibitors, contraceptives
- Dose
  - 500 mcg PO daily

Belatacept (Nujolix®)

- Organ rejection – kidney transplant
- Literature
  - Efficacy failure: 21.7% vs 16.7%
- Warnings and ADRs
  - Posttransplant lymphoproliferative disorder [BW], progressive multifocal leukoencephalopathy [PML], malignancies [BW], serious infections [BW]
  - Anemia, N, V, D, UTI, edema, constipation, headache, pyrexia, graft dysfunction
- Drug Interactions
  - Medications that may be affected by immunosuppression
- Dose
  - 10 mg/kg IV days 1 and 5; weeks 2 and 4; weeks 8 and 12
  - 5 mg/kg IV week 16; then every 4 weeks
  - *Infuse over 30 minutes; low-protein-binding filter

Quick Stop Question 4

- For a number of these medications, there are significant interactions with the CYP enzyme system.
- What herbal medication is contraindicated or should be used with caution in medications that are metabolized by CYP3A4?

http://www.polleverywhere.com/multiple_choice_polls/CTE3MGpGMOU5Nuk

OTHER DISEASE STATES OR INDICATIONS
**Linagliptin (Tradjenta™)**

- Type II diabetes
- Literature: change in A1C
  - Monotherapy: -0.4% vs -0.1%
  - Combination
    - Metformin: -0.5% vs 0.15%
    - Glimpiride: -0.4% vs -0.6%
    - Pioglitazone: -1.1% vs -0.6%
    - Sulfonylureas: -0.5% vs 0.1%
- Metformin + sulfonylureas: 0.7% vs -0.1%
- Warnings and ADRs
  - Nasopharyngitis, hypoglycemia, pancreatitis
- Drug Interactions
  - Strong CYP3A4 and P-glycoprotein inducers, sulfonylureas
  - Ethanol; herbs/nutriceuticals with hypoglycemic properties
- Dose
  - 5 mg PO daily

**Vilazodone (Viibryd™)**

- Major depressive disorder
- Literature
  - Superior to placebo in MADRS – 8 weeks
    - Change from baseline: -3.2 (study 1); -2.5 (study 2)
- Warnings and ADRs
  - Suicidal thinking/behavior [BW], serotonin syndrome, neuroleptic malignant syndrome, abnormal bleeding, hyponatremia
  - N, V, O, insomnia
- Drug Interactions
  - MAOI inhibitors, CYP3A4 inhibitors/inducers, serotonergic drugs, aspirin, NSAIDs
- Dose
  - Titrate up to 40 mg PO daily [with food]
    - Dose adjustments for strong and moderate CYP3A4 inhibitors

**Ezogabine (Potiga™)**

- Adjunctive treatment of partial onset seizures
- Literature
  - Reduction in 28-day seizure frequency
- Warnings and ADRs
  - Neuropsychiatric symptoms, urinary retention, QT prolongation, suicidal ideation
  - Dizziness, somnolence, fatigue,
- Drug Interactions
  - Phenytoin, carbamazepine, digoxin
- Dose
  - Titrate up to 400 mg PO three times daily
    - Dose adjustments in renal failure and geriatric patients

**Clobazam (Onfi™)**

- Seizures associated with Lennox-Gastaut syndrome
- Literature
  - Reduction in weekly frequency of drop seizures and overall seizure frequency
- Warnings and ADRs
  - Somnolence; sedation, drooling, constipation, aggression, insomnia, dysarthria, fatigue
- Drug Interactions
  - CNS depressants, CYP3A4 substrates
- Dose
  - Titrate up to 20 mg PO twice daily
    - Dose adjustments for hepatic impairment and CYP2C19 poor metabolizers

**Afiblercept (Eylea™)**

- Neovascular (wet) age-related macular degeneration
- Literature
  - Maintained vision: ≥ 95% in all treatment arms
- Warnings and ADRs
  - Endophthalmitis, retinal detachments, increased intraocular pressure
  - Conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters
- Drug Interactions
  - None reported
- Dose
  - 2-mg intravitreal injection
    - Every 4 weeks [3 months]; every 8 weeks [2 months]

**Icatinant (Firazyr®)**

- Acute attacks of hereditary angioedema
- Literature
  - Median time to 50% reductions: ≈2 h vs 19 h
- Warnings and ADRs
  - Injection site reactions, pyrexia, dizziness, rash, transaminase increase
- Drug Interactions
  - Potential: ACE inhibitors
- Dose
  - 30 mg SC [at 6 hour intervals if needed]
    - No more than 3 injections per 24 h
NEW DOSAGE FORMS

 Azilsartan/chlorthalidone (Edarbyclor™)
 Bupivacaine liposome injectable suspension (Exparel®)
 Bupropion extended release (Forfivo XL)
 Emtricitabine/tenofovir (Complera™)
 Fentanyl sublingual tablets (Abstral™)
 Fentanyl nasal spray (Lazanda™)
 Gabapentin encarbil (Horizant™)
 Gabapentin (Gralise™)
 Ibuprofen/famotidine (Duexis®)
 Ipratropium/albuterol (Combivent® Respimat®)
 Nevirapine extended release (Viramune® XR™)
 Nitroglycerin (Rectiv™)
 Oxycodone (Oxecta®)
 Zolpidem sublingual tablet (Intermezzo®)

MEDICATION SAFETY ALERTS

 Acetaminophen – limit to 325 mg/dosage unit
 Citalopram – abnormal heart rhythms
 Dabigatran – serious post marketing bleeding events
 Drosipirenone – increased risk of blood clots
 Drotrecogin alfa – market withdrawal
 Fluconazole – treatment associated with birth defects
 Ipilimumab – severe immune-mediated reactions
 Lansoprazole ODT – clogged oral syringes/feeding tubes
 Linezolid – serious CNS reactions with psychiatric medications
 Lopinavir/ritonavir – premature babies
 Rosiglitazone – REMS
 Simvastatin – label and dose changes
 SSRIs – use during pregnancy
 Varenicline – risk of cardiovascular events

What’s on the Horizon

2012 Pipeline

 Approvals
 – Axitinib (Inlyta®)
 – Glucarpidase (Voraxne®)
 – Ingenol mebutate (Picato®)
 – Ivacaftor (Kalydeco™)
 – Mifepristone (Korlym™)
 – Tafluprost (Zioptan™)
 – Vismodegib (Erivedge™)
2012 Pipeline

• AHJP: Projecting future drug expenditures – 2012
  – Aclidinium bromide – COPD
  – Apixaban – anticoagulant
  – Carfilzomib – multiple myeloma
  – Drozidopa – symptomatic neurogenic orthostatic hypotension
  – Linacotide – irritable bowel syndrome
  – Lucinactant – respiratory distress syndrome in prematurity
  – Pedisate – anemia in chronic kidney disease
  – Pixantrone – non-Hodgkin’s lymphoma
  – Ridaforolimus – sarcoma
  – Taliglucerase alfa – Gaucher disease
  – Vincristine liposomes – acute lymphocytic leukemia

Staying Current

• FDA CDER:
  – http://www.fda.gov/Drugs/default.htm
  – Listserv or RSS Feeds
  – Drugs@FDA
• Medscape
  – www.medscape.com
• CenterWatch
  – http://www.centerwatch.com/

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