New Drugs Update: FDA Approvals for 2016-17

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MPA Fall Meeting (October 1, 2017)

Disclosure

- I will discuss off label use or investigational use in my presentation.
- I have no financial relationships to disclose.

Goals & Objectives

GOAL:

- To review selected entities approved by the Food & Drug Administration in 2016-17

OBJECTIVES:

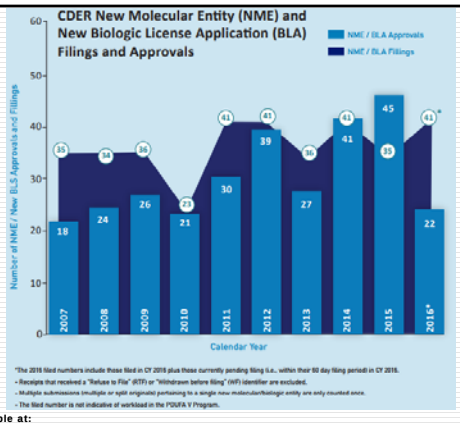
- List the name, mechanism of action, pharmacological properties, route of administration, dosing schedule, and dosage forms for the new drugs reviewed
- Discuss cautions, side effects, potential drug interactions, and primary points of patient education for these medications
- Review the disease states where these medications are being used
- Compare and contrast their role in practice with existing medications prescribed for similar indications

New Drug Application Designation

Number	Meaning
1	New molecular entity
2	New active ingredient
3	New dosage form
4	New combination
5	New formulation or new manufacturer
6	New indication
7	Drug already marketed without an approved NDA
8	OTC switch
10	New indication submitted as distinct NDA

Letter	Meaning
P	Priority review drug
S	Standard review drug
O	Orphan drug

Additional Methods for Expediting Approval
Fast Track
Breakthrough
Priority Review
Accelerated Approval
Qualified Infectious Disease Product



Available at:
https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf. Accessed August 2017.

2016 Approvals

- 22 NME/BLA (41 applications filed)
- First-in-class (N=8): Defitelio, Zinbryta
- Rare diseases (N=9): Exondys 51, Spinraza
- Fast Track (N=8): Epclusa, Lartruvo
- Breakthrough (N=7): Epclusa, Zepatier
- Priority Review (N=15): Epclusa, Tecentriq
- Accelerated Approval (N=6): Exondys 51, Lartruvo

2017 Novel Drug (NME/BLA) Approvals

- Plecanatide (Trulance®): chronic idiopathic constipation in adults
- Etelcalcetide (Parsabiv®): secondary hyperparathyroidism in adults with CKD on HD
- Deflazacort (Emflaza®): Duchenne muscular dystrophy
- Brodalumab (Siliq®): moderate to severe plaque psoriasis
- Telotristat (Xermelo®): carcinoid syndrome diarrhea
- Ribociclib (Kisqali®): postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer
- Safinamide (Xadago®): Parkinson's disease experiencing "off" episodes (adjunctive)
- Naldemedine (Symproic®): OIC in adults with non-cancer pain
- Avelumab (Bavencio®): metastatic Merkel cell carcinoma; locally advanced or metastatic urothelial carcinoma
- Niraparib (Zejula®): maintenance treatment for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Ocrelizumab (Ocrevus®): relapsing or primary progressive forms of multiple sclerosis
- Dupilumab (Dupixent®): moderate to severe atopic dermatitis
- Deutetrabenazine (Austedo®): chorea associated with Huntington's disease
- Valbenazine (Ingrezza®): tardive dyskinesia

Updated 8/30/16.

2017 Novel Drug (NME/BLA) Approvals

- Cerliponase alfa (Brineura®): infantile neuronal ceroid lipofuscinosis type 2
- Midostaurin (Rydapt®): newly diagnosed AML that is FLT3 mutation-positive
- Abaloparatide (Tymlos®): postmenopausal women with osteoporosis
- Brigatinib (Alunbrig®): anaplastic lymphoma kinase-positive metastatic NSCLC
- Durvalumab (Imfinzi®): locally advanced or metastatic urothelial carcinoma
- Edaravone (Radicava®): amyotrophic lateral sclerosis
- Sarilumab (Kevzara®): moderate to severe active rheumatoid arthritis
- Delafloxacin (Baxdela®): acute bacterial skin and skin structure infections (ABSSSI)
- Betrixiban (Bevyxxa®): VTE prophylaxis in adult hospitalized patients
- Guselkumab (Tremfya®): moderate to severe plaque psoriasis
- Neratinib (Nerlynx®): early stage HER2-overexpressed/amplified breast cancer
- Sofosbuvir/velpatasvir/voxilaprevir (Vosevi®): chronic HCV infection (genotypes 1-6)
- Enasidenib (IDHIFA®): relapsed or refractory AML with IDH2 mutation
- Glecaprevis/pibrentasvir (Mavyret®): chronic HCV infection (genotypes 1-6)
- Inotuzumab ozogamicin (Besponsa®): relapsed or refractory B-cell precursor ALL
- Benznidazole: Chagas disease caused by *Trypanosoma cruzi*
- Meropenem/vaborbactam (Vabomere®): complicated UTI in adults

Updated 8/30/16.

2017 Other Notable FDA Approvals

- Morphine (Arymo ER®): severe pain
- Hydrocodone (Vantrela ER®): severe pain
- Ephedrine (Corphedra®): hypotension from anesthesia
- Nitroprusside premade bag (Nipride RTU®): hypertension
- Oxycodone (Roxybond®): severe pain
- Infliximab-abda (Renflexis®): multiple indications
- Adalimumab-adbm (Cyltezo®): multiple indications
- Epinephrine prefilled syringe (Symjepi®): anaphylaxis
- Rituximab/hyaluronidase (Rituxan Hycela®): multiple indications (subcutaneous use only)

Updated 9/6/16.

FDA Drug Safety Communications

- 6/23/17: single entity injectables (removal of ratio expressions of strength)
- 5/22/17: no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs
- 5/16/17: confirms increased risk of leg and foot amputations with canagliflozin
- 4/27/17: label changes for use of general anesthetic and sedation drugs in young children
- 4/20/17: restricted use of codeine and tramadol in children; recommends against use in breastfeeding women
- 2/2/17: rare but serious allergic reactions to chlorhexidine gluconate
- 12/12/16: pioglitazone may be linked to increased risk of bladder cancer
- 10/4/16: hepatitis B reactivating in some patients treated for hepatitis C
- 8/31/16: opioid and benzodiazepine combination [boxed warning]
- 7/26/16: fluoroquinolone restriction update
- 5/12/16: fluoroquinolone restriction recommendations due to disabling side effects
- 3/22/16: safety issues with opioid pain medicines (label changes)

Available at: http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm.
Accessed August 2017.

Topics for Today's Presentation

- Abuse-deterrent opioid updates
- Biosimilars update
- Delafloxacin (Baxdela®)
- Betrixaban (Bevyxxa®)
- Plecanatide (Trulance®)
- Naldemedine (Symproic®)

RJ1

Abuse-deterrent Opioid Updates

- Recent FDA approvals
  - 1/9/17: Morphine (Arymo ER®)
  - 1/17/17: Hydrocodone (Vantrela ER®)
  - 4/20/17: Oxycodone (RoxyBond®)
- June 8, 2017: FDA requests Endo remove Opana ER from the market
- July 6, 2017: Endo voluntarily removed Opana ER from the market
- July 7, 2017: industry-funded group petitions FDA to withdraw approvals of non-abuse-deterrent opioids by 2020

Available at: https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm
Accessed August 2017.

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RJ1 reference FDA website including summary timeline from 1995 to present.
Rebecca Jones, 8/29/2017

FDA-approved Abuse Deterrent Formulations

Brand Name	Formulation	FDA Approval	Company
Troxyca ER	Oxycodone/naltrexone ER capsules	8/19/16	Pfizer
Embeda	Morphine/naltrexone ER capsules	8/13/09	Alpharma
Hysingla ER	Hydrocodone ER tablets	11/20/14	Purdue
Targiniq ER	Oxycodone/naloxone ER tablets	7/23/14	Purdue *(no current marketing plans)*
Xtampza ER	Oxycodone ER capsules	4/26/16	Collegium Pharm
MorphaBond ER	Morphine ER tablets	10/2/15	IDT
OxyContin	Oxycodone ER tablets	4/5/10	Purdue
Arymo ER	Morphine ER tablets	1/9/17	Egalet
Vantrela ER	Hydrocodone ER tablets	1/17/17	Teva
RoxyBond	Oxycodone IR tablets	4/20/17	Inspirion Delivery

Abuse-deterrent Features

- Physical or chemical barriers
- Combinations that reduce euphoria
- Aversion techniques
- Delivery systems
- Prodrug formulations
- Combination of the above

Abuse-deterrent Studies

- Laboratory-based in vitro manipulation and extraction studies (Category 1)
- Pharmacokinetic studies (Category 2)
- Clinical abuse potential studies (Category 3)
  - oral, intranasal, and simulated IV abuse potential
- Package labeling: study data detailed in section 9 (DRUG ABUSE AND DEPENDENCE)

FDA-approved Products for Treating Opioid Addiction and Overdose

- Reversal options for first responders/primary caregivers
  - Naloxone (Evzio®) auto-injector-2014
  - Naloxone (Narcan®) nasal spray-2015
- Medication-Assisted Treatment (MAT) options
  - Buprenorphine
    - Oral (Suboxone®, Subutex®)-2002
    - Transdermal (Butrans®)-2010
    - Sublingual (Zubsolv®)-2013
    - Buccal (Bunavail®, Belbuca®)-2014/15
    - Implant (Probuphine®)-2016
  - Methadone (Dolophine®, Methadose®)-1947/73
  - Naltrexone (Vivitrol®) ER intramuscular injection-2006

Biosimilar Resources

- FDA webpage on biosimilars
  - Biologics Price Competition and Innovation Act of 2009
  - Draft guidance for industry
    - Nonproprietary naming of biological products (August 2015)
    - Labeling, statistical approaches to evaluation of analytics similarity data, and considerations in demonstrating interchangeability to a referenced product
  - FDA Purple Book
- ASHP Resource Centers, Emerging Sciences, Biosimilars

State Laws and Legislation Related to Biosimilars

- As of July 3, 2017, laws have been enacted in 35 states and Puerto Rico
  - FDA approval to state "interchangeable"
  - Prescriber decides (i.e., DAW)
  - Notification vs. communication
  - Records of substitution
  - Pharmacist immunity
- Michigan House Bill 4812 (2015)
  - Passed in House on November 10, 2015
  - Last reported in Senate Health Policy Committee on 2/18/16 with recommendation for bill to pass

Available at: http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx. Accessed September 2017.

Biosimilars

- FDA-approved biosimilars
  - Filgrastim-sndz (Zarxio®) by Sandoz: 3/6/15
  - Infliximab-dyyb (Inflectra®) by Celltrion/Pfizer: 4/5/16
  - Infliximab-abda (Renflexis®) by Samsung Bio/Merck: 4/21/17
  - Etanercept-szzs (Erelzi®) by Sandoz: 8/30/16
  - Adalimumab-atto (Amjevita®) by Amgen Inc: 9/23/16
  - Adalimumab-adbm (Cyltezo®) by Boehringer Ingelheim: 8/25/17
  - Insulin lispro (Admelog®) by Sanofi (tentative approval)
- On the horizon
  - Epoetin alpha, filgrastim, infliximab, pegfilgrastim
  - Oncologic mAbs (bevacizumab, rituximab, trastuzumab)

Systemic Fluoroquinolones

Generic Name	Trade Name	FDA-approval Date	Available?
Nalidixic acid	NegGram	1964	No
Cinoxacin	Cinobac	1980	No
Norfloxacin	Noroxin	1986	No
Ciprofloxacin	Cipro	1987	Yes
Ofloxacin	Floxin	1990	Yes
Enoxacin	Penetrex	1991	No
Temafloxacin	Omniflox	1992	No
Lomefloxacin	Maxaquin	1992	No
Levofloxacin	Levaquin	1996	Yes
Sparfloxacin	Zagam	1996	No
Grepafloxacin	Raxar	1997	No
Trovafloxacin/alatrovafloxacin	Trovan	1997	No
Moxifloxacin	Avelox	1999	Yes
Gatifloxacin	Tequin	1999	No
Gemifloxacin	Factive	2003	Yes

Delafloxacin (Baxdela®)

- FDA approval: June 19, 2017
  - New Molecular Entity
  - Priority review drug
  - QIDP
- Marketed by: Melinta Therapeutics, Inc.
- Website information: http://www.baxdela.com

Delafloxacin

RJ3

- Mechanism of action: dual inhibition of DNA gyrase and topoisomerase IV
- FDA-labeled indication: treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria
- Dosage form/strength:
  - Injection: 300 mg delafloxacin (equivalent to 433 mg delafloxacin meglumine) as a lyophilized powder in a single dose vial
  - Oral tablets: 450 mg delafloxacin (equivalent to 649 mg delafloxacin meglumine)

Dosing and Administration

- Dose:
  - Injection: 300 mg IV over 60 minutes every 12 hours
  - Oral: 450 mg PO every 12 hours
  - Recommended duration: 5 to 14 days
- Dose adjustment:
  - eGFR 30-89 mL/min/1.73 m^2: no dosage adjustment
  - eGFR 15-29 mL/min/1.73 m^2: 200 mg every 12 hrs (IV), no dosage adjustment for PO
  - ESRD: not recommended
  - *In patients with severe renal impairment or ESRD, accumulation of the IV vehicle, sulfobutylether-β-cyclodextrin occurs*

Dosing and Administration

- Injection must be reconstituted and further diluted using D5W or NS
  - Reconstituted with 10.5 mL to yield 25 mg/mL
  - Clear yellow to amber colored solution
  - Dilute to a total volume of 250 mL for a 1.2 mg/mL concentration
  - Reconstituted powder may be stored for up to 24 hours under refrigerated or controlled room temperature

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RJ3 anioinc structure may enhance its potency in acidic environments, such as at an infection site
Rebecca Jones, 8/29/2017

Pipeline Indications

- Community-acquired bacterial pneumonia
  - Phase 3 study vs moxifloxacin/linezolid
  - NCT02679573 currently recruiting
- cUTI (phase 2)
- Uncomplicated gonorrhea
  - Single dose, phase III study vs ceftriaxone
  - PROCEEDING (NCT02015637) study terminated based on interim review that found delafloxacin may not be sufficient to treat some patients

Pharmacokinetics

Parameter	Value
Bioavailability	58.8%
Tmax	0.75-1 hrs
Protein Binding (VoD)	84% (30-48 L)
Food effect	Not significant
Metabolism	Glucuronidation (UGT1A1, UGT1A3, UGT2B15)
Elimination half-life	3.7 hrs

Antimicrobial Activity

- Gram-positive pathogens
  - *E. faecalis,* viridans group stretococci
  - MRSA, MR-CoNS, beta-hemolytic streptococci
  - FQ-resistant strains of *S. aureus*, CoNS, *S. pneumoniae*
- Gram-negative pathogens
  - *H. influenzae, M. catarrhalis, K. oxytoca*
  - *Enterobacter* spp., *Enterobacteriaceae*
  - *E. coli, K. pneumoniae, P. aeruginosa, Acinetobacter* spp. (limited)
- Anaerobes and atypical respiratory tract pathogens

Source: Pfaller MA, et al. In vitro activity of delafloxacin against contemporary bacterial pathogens from the United States and Europe, 2014. Antimicrob Agents Chemother. 2017;61(4).

IDSA Guidelines

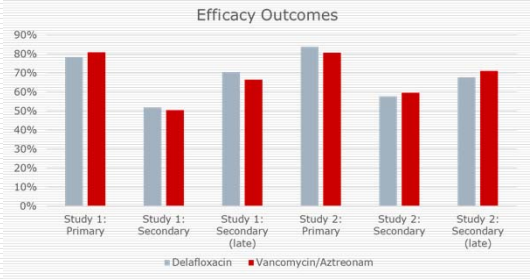
- Skin and soft tissue infections 2014
  - Purulent vs. nonpurulent
  - Severity (mild, moderate, severe)
  - Empiric vancomycin reserved for severe infections or MRSA rates higher
- MRSA infections 2011
  - FQs may have activity against some CA-MRSA isolates, but they are not routinely recommended, because resistance may emerge with monotherapy.

ABSSSI Studies

- Two phase III, multicenter, double-blind, non-inferiority trials (N=1,510 total)
  - Trial 1 (NCT01811732): delafloxacin 300 mg IV q12 hrs
  - Trial 2 (NCT01984684): delafloxacin 300 mg IV q12 hrs x6 doses then 450 mg PO q12 hrs
  - Comparator group: vancomycin 15 mg/kg + aztreonam (d/c if no GNP identified from baseline cultures)
  - Both groups were to receive 10-28 doses of study drug
- Primary outcome measures
  - Clinical response at 48 to 72 hours post initiation of treatment defined as a 20% or greater decrease in lesion size as determined by digital planimetry of the leading edge of erythema
- Secondary outcome measures
  - Investigator-assessed response of signs and symptoms of infection at the follow up visit (study day 14 ± 1)
  - Investigator-assessed response of signs and symptoms of infection at the late follow up visit (study day 21 to 28)

Available at: www.clinicaltrials.gov
Accessed: August 2017.

ABSSSI Studies



Contraindications/ Black Box Warnings

- Contraindications: known hypersensitivity to delafloxacin or other fluoroquinolones
- Black box warnings
  - Tendinitis and tendon rupture
  - Peripheral neuropathy
  - Central nervous system effects
  - May exacerbate muscle weakness in patients with myasthenia gravis

Warnings/Precautions/Adverse Reactions

- Hypersensitivity reactions
- *Clostridium difficile*-associated diarrhea
- Development of drug-resistant bacteria
- Most common adverse reactions (incidence ≥2%)
  - nausea, diarrhea, vomiting
  - headache
  - transaminase elevations

Drug Interactions

- Chelation agents: antacids, sucralfate, metal cations (iron), multivitamins (iron, zinc)
- Delafloxacin oral should be taken at least 2 hours before or 6 hours after

Patient Counseling

- Serious adverse reactions (i.e., tendinitis and tendon rupture, peripheral neuropathy, exacerbation of myasthenia gravis)
- Administration with food and concomitant medications
  - With or without food and without any dietary restrictions
  - 2 hours before or 6 hours after antacids, sucralfate, metal cations, multivitamins
- Should tell physicians if they are pregnant or plan to become pregnant or are breastfeeding.
- Missed doses: dose should be taken as soon as possible up to 8 hours before the next dose and resume normal dosing schedule the following day. Do not double doses.

Betrixaban (Bevyxxa®)

- FDA approval: June 23, 2017
  - New Molecular Entity
  - Priority review drug
- Marketed by: Portola Pharmaceuticals
- Website information: http://www.bevyxxa.com

Betrixaban

- Mechanism of action: factor Xa inhibitor
- FDA-labeled indication:
  - Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE
- Dosage form/strength:
  - 40 mg and 80 mg capsules

Dosing and Administration

- Route: oral
- Dose:
  - Initial: 160 mg
  - Maintenance: 80 mg once daily (taken at same time each day with food)
  - Recommended duration: 35-42 days
- Dose adjustment:
  - Clcr ≥15 to <30 mL/min: 80 mg once then 40 mg daily
  - Concomitant P-gp inhibitors: 80 mg once then 40 mg daily

Factor Xa Inhibitor Comparison

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
FDA Approval	Xarelto® July 2011	Eliquis® December 2012	Savaysa® January 2015	Bevyxxa® June 2017
Atrial fibrillation	Yes	Yes	Yes	No
DVT/PE treatment	Yes	Yes	Yes	No
DVT prophylaxis (knee/hip replacement)	Yes	Yes	No	No
VTE prophylaxis in medical pts	No	No	No	Yes

Factor Xa Inhibitor Comparison

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Bioavailability	10 mg (80-100%) 20 mg (66%)	50%	62%	34%
Tmax	2-4 hrs	3-4 hrs	1-2 hrs	3-4 hrs
Protein Binding	92-95%	87%	55%	60%
Food effect	15 mg, 20 mg take with food 10 mg take with or without food	Not significant	Not significant	Take with food
Metabolism	CYP3A4/5, CYP2J2	CYP3A4 1A2, 2C8, 2C9, 2C19, 2J2	Minimal	Minimal
Elimination half-life	5-9 hrs	12 hrs	10-14 hrs	19-27 hrs

Factor Xa Inhibitor Comparison

	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Contra-indications	• Active pathological bleeding • Hypersensitivity to ingredients			
Warnings/ Precautions	**Black Box Warning** • Premature discontinuation • Spinal/epidural hematoma Other Warnings/ Precautions • Risk of bleeding • Prosthetic heart valves • Pregnancy related hemorrhage	**Black Box Warning** • Premature discontinuation • Spinal/epidural hematoma Other Warnings/ Precautions • Risk of bleeding • Prosthetic heart valves	**Black Box Warning** • Reduced efficacy in nonvalvular a-fib with Clcr >95 mL/min • Premature discontinuation • Spinal/epidural hematoma Other Warnings/Precautions • Risk of bleeding • Prosthetic heart valves	**Black Box Warning** • Spinal/epidural hematoma Other Warnings/ Precautions • Risk of bleeding • Severe renal impairment • Concomitant P-gp inhibitors
Drug Interactions	• CYP450 3A4 and P-glycoprotein inhibitors/inducers • Anticoagulants • NSAIDs/Aspirin/Platelet Aggregation Inhibitors		• P-glycoprotein inhibitors/inducers • Anticoagulants • NSAIDs/Aspirin/Platelet Aggregation Inhibitors	

VTE Prophylaxis in Medically Ill Patients

- CHEST guideline summary (2012, 9th ed)
  - Acutely ill hospitalized medical patients at increased risk of thrombosis recommend using LMWH, LDUF bid/tid, or fondaparinux (Grade 1B)
  - Suggest against extending duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B)
  - EXCLAIM part of guideline review
- Other studies evaluating extended duration
  - ADOPT (apixaban vs. enoxaparin)-NEJM 2011
  - MAGELLAN (rivaroxaban vs. enoxaparin)-NEJM 2013

ADOPT STUDY

- Apixaban 2.5 mg bid for 30 days vs. enoxaparin 40 mg once daily for 6-14 days
- 6,528 medically ill patients (apix vs. enox)
  - Hospitalized for respiratory failure: 37.1% and 37.1%
  - Hospitalized for HF: 39% and 38.1%
  - Hospitalized for infection: 21.5% and 22.8%
  - No D-dimer levels reported
  - Age of 75 yrs or older: 29.6% and 29.9%
  - History of cancer: 9.6% and 9.8%
  - History of VTE: 4.3% and 3.8%
- Primary efficacy: 30 day composite of death related to VTE/ PE, symptomatic DVT, or asymptomatic proximal leg DVT
- Primary safety: major bleeding

Source: Goldhaber SZ, et al; ADOPT Investigators. Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients. N Engl J Med. 2011;365(23):2167-77.

MAGELLAN STUDY

- Rivaroxaban 10 mg once daily for 35±4 days vs. enoxaparin 40 mg once daily for 10±4 days
- 8,101 medically ill patients (riva vs. enox)
  - Hospitalized for respiratory insufficiency: 27.3% and 28.7%
  - Hospitalized for HF: 32.3% and 32.4%
  - Hospitalized for infection: 45.8% and 45.1%
  - Median D-dimer level was 0.94 and 0.95
  - Age of 75 yrs or older: 38.3% and 38.6%
  - History of cancer: 17.3% and 16.7%
  - History of VTE: 5% and 4.4%
- Primary efficacy: composite of asymptomatic proximal DVT, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or VTE death up to day 10 (noninferiority test) and up to day 35 (superiority test)
- Primary safety: composite of major or clinically relevant nonmajor bleeding

Source: Cohen AT, et al; MAGELLAN Investigators. Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients. N Engl J Med. 2013;368(6):513-23.

APEX STUDY

- Phase III randomized, placebo-controlled, multicenter study
  - Betrixaban 80 mg PO once daily for 35 to 42 days (loading dose of 160 mg)
  - Enoxaparin 40 mg SQ once daily for 10 ± 4 days
- 7,513 medically ill patients (betrix vs. enox)
  - Hospitalized for respiratory failure: 11.9% and 12.6%
  - Hospitalized for HF: 44.6% and 44.5%
  - Hospitalized for infection: 29.6% and 28.2%
  - Elevated D-dimer level (≥2x ULN): 62.3% and 62.1%
  - Age of 75 yrs or older: 68.5% and 67%
  - History of cancer: 12.4% and 11.8%
  - History of VTE: 8.3% and 7.9%

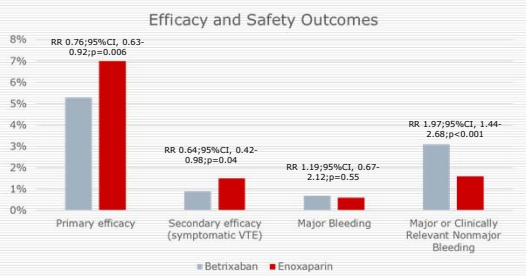
Source: Cohen AT, et al; APEX Investigators. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med. 2016;375(6):534-44.

APEX STUDY

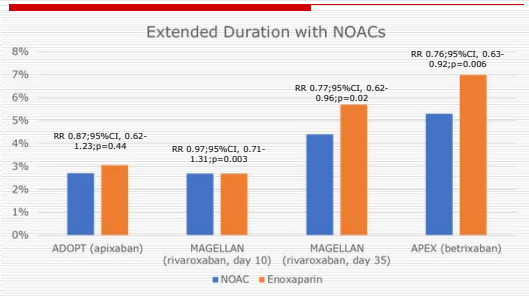
- Cohort 1: patients with an elevated D-dimer level
- Cohort 2: patients with an elevated D-dimer level or an age of at least 75 years
- Overall cohort: all the enrolled patients
- Outcome measures
  - Primary: composite of asymptomatic proximal DVT between day 32 and day 47, symptomatic proximal or distal DVT, symptomatic nonfatal PE, or death from VTE between day 1 and day 42
  - Secondary: composite of death from VTE, nonfatal PE, or symptomatic DVT between day 1 and day 42
- Primary safety outcome
  - Occurrence of major bleeding at any point until 7 days after the discontinuation of all study medications
  - Bleeding events classified (ISTH) as major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding

Source: Cohen AT, et al; APEX Investigators. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. N Engl J Med. 2016 Aug 11;375(6):534-44.

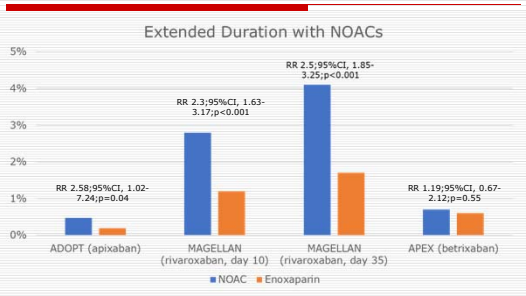
APEX Study



Primary Efficacy Outcomes



Primary Safety Outcomes



MAGELLAN Study major bleeding rates:
At day 10: 0.6% (riva), 0.3% (enox): RR 2.2;95% CI 1.07-4.45;p=0.03
At day 35: 1.1% (riva), 0.4% (enox): RR 2.9;95% CI 1.6-5.15;p<0.001

MARINER STUDY (NCT02111564)

- Randomized, double-blind, placebo-controlled (N≈8,000 pts)
- Medically ill patients at least 40 years of age hospitalized for 3-10 days receiving UFH or LMWH prophylaxis
- IMPROVE VTE risk score combined with D-dimer
  - IMPROVE VTE risk score ≥4; or
  - Risk score of 2-3 and a D-dimer level >2x ULN
- Rivaroxaban 10 mg once daily for 45 days vs. placebo at hospital discharge
- Primary efficacy: composite of symptomatic VTE and VTE-related death
- Primary safety: major bleeding

Source: Raskob GE, et al. The MARINER trial of rivaroxaban after hospital discharge for medical patients at high risk of VTE. Design, rationale, and clinical implications. Thromb Haemost 2016;115(6):1240-8.

Other Betrixaban Clinical Trials

- Atrial fibrillation
  - NCT00742859 (phase II vs. warfarin for prevention of stroke in patients with atrial fibrillation
- Prevention of DVT/PE
  - NCT00375609 (phase II vs. enoxaparin for prevention of thrombosis-related events following total knee arthroplasty)

Patient Counseling

- May take longer than usual for bleeding to stop, may bruise/bleed more easily.
- Do not discontinue without talking to their physician first.
- Should tell physicians/dentists they are taking oral anticoagulant and/or any other product known to affect bleeding before procedures.
- Should tell physicians if they are pregnant or plan to become pregnant or are breastfeeding.
- Missed doses: dose should be taken as soon as possible on the same day and resume normal dosing schedule the following day. Do not double doses.
- Take at same time each day with food.

Evidence-based Treatment of Chronic Idiopathic Constipation

- 2014 American College of Gastroenterology Monograph
  - Irritable Bowel Syndrome (IBS)
  - Chronic Idiopathic Constipation (CIC)
- Strong recommendation (quality of evidence)
  - Fiber (low)
  - PEG (high)
  - Lactulose (low)
  - Sodium picosulfate and bisacodyl (moderate)
  - Linaclotide (high)
  - Lubiprostone (high)

Available at: http://gi.org/acg-institute/evidence-based-reviews/. Accessed August 2017.

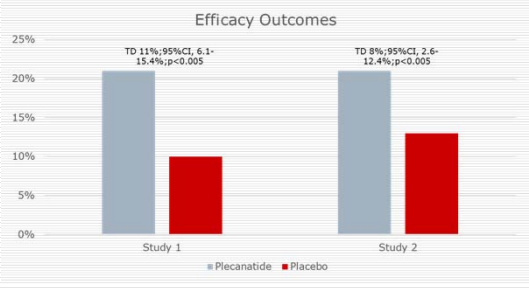
Plecanatide (Trulance®)

- FDA approval: January 19, 2017
  - New Molecular Entity
  - Standard review drug
- Marketed by: Synergy Pharmaceuticals
- Website information: http://www.trulance.com

Plecanatide

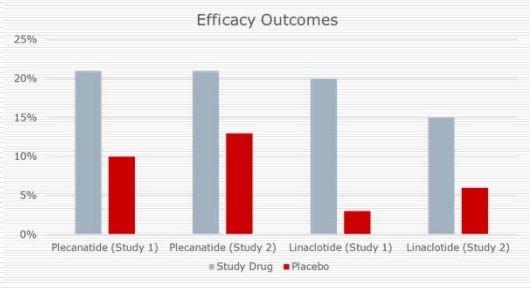
- Mechanism of action:
  - guanylate cyclase-C agonist (amino acid peptide)
  - Acts locally on the luminal surface of the intestinal epithelium
  - Increase intracellular and extracellular concentrations of cGMP which stimulates secretion of chloride and bicarbonate into the intestinal lumen
- FDA-labeled indication:
  - Treatment of chronic idiopathic constipation in adults
- Clinical studies
  - Two 12 week, randomized, double-blind, placebo-controlled, multicenter studies (NCT1982240 and NCT02122471)
  - 1,775 patients with modified Rome III criteria CIC for ≥3 months
  - Plecanatide 3 mg and 6 mg vs. placebo

Plecanatide CIC Studies



Note: Both studies included a 6 mg daily arm that did not demonstrate additional treatment benefit and had a greater incidence of adverse reactions compared to 3 mg daily.

Guanylate Cyclase-C Agonists for CIC



Primary efficacy: patient with ≥3 CSBM/week and an increase of at least 1 CSBM from baseline in a given week for ≥9 out of the 12 week treatment period.

Pipeline Indications

- Irritable bowel syndrome with constipation (IBS-C)
  - 12 week studies evaluating 3 mg and 6 mg vs. placebo
  - Two phase III studies currently recruiting
    - NCT02387359
    - NCT02493452
- Adolescents 12 to <18 years of age with chronic idiopathic constipation
  - Phase II study evaluating doses of 0.5 mg, 1 mg, 1.5 mg vs. placebo
  - NCT03120520 currently recruiting

Dosing and Administration

- Dosage form/strength:
  - 3 mg tablets
- Dose:
  - Oral: 3 mg PO once daily
  - May be taken with or without food
  - Tablets can be crushed and administered either in applesauce or with water
  - Can be administered with water via nasogastric or gastric feeding tube
- Dose adjustment:
  - No dosage adjustments provided

Pharmacokinetics

Parameter	Linaclotide	Plecanatide
Bioavailability	Minimal	Minimal
Tmax	N/A	N/A
Protein Binding	N/A	N/A
Food effect	High fat meal resulted in looser stools and higher stool frequency (*take on empty stomach*)	Not significant
Metabolism	In GIT to active metabolite, both proteolytically degraded	
Elimination half-life	N/A	N/A

Contraindications/ Black Box Warnings

- Contraindications:
  - Patients less than 6 years of age due to the risk of serious dehydration
  - Patients with known or suspected mechanical gastrointestinal obstruction
- Black box warnings
  - Contraindicated in patients less than 6 years of age
  - Avoid use in patients 6 years to less than 18 years of age

Warnings/Precautions/Adverse Reactions

- Diarrhea (if severe, suspend dosing and rehydrate the patient)
- Most common adverse reactions (incidence ≥2%)
  - Diarrhea
  - Sinusitis, upper respiratory tract infection, abdominal distension, flatulence, abdominal tenderness, increased ALT >5-15 times ULN

Patient Counseling

- Diarrhea: stop Trulance and contact healthcare provider if they experience severe diarrhea.
- Accidental ingestion especially in children.
- Take once daily with or without food.
- Information on administration to patients with swallowing difficulties.
- Should tell physicians if they are pregnant or plan to become pregnant or are breastfeeding.
- Missed dose should be skipped and resume normal dosing schedule the following day. Do not double doses.
- Proper storage (i.e., 68ºF to 77ºF).

Opioid-Induced Constipation Treatment Options

- Dietary fiber, fluid intake, physical activity
- Laxatives, stimulants, stool softeners, osmotic agents
- Secretagogues (lubiprostone-2006)
- PAMORAs (Peripherally Acting Mu-Opioid Receptor Antagonists)
  - Methylnaltrexone injection (2008)—*GEQ tentative*
  - Methylnaltrexone tablet (2016)
  - Naloxegol tablet (2014)
  - Alvimopan (not indicated for OIC)

Naldemedine (Symproic®)

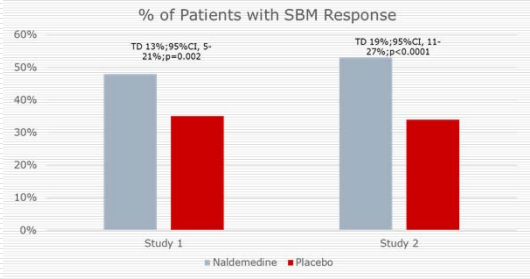
- FDA approval: March 23, 2017
  - New Molecular Entity
  - Standard review drug
  - Schedule II narcotic
- Marketed by: Purdue Pharmaceuticals
- Website information: not available

Symproic®

Naldemedine

- Mechanism of action:
  - Peripherally-acting mu-opioid receptor antagonist
  - Derivative of naltrexone with added side chain to increase molecular weight and polar surface area
- FDA-labeled indication:
  - Treatment of opioid-induced constipation in adults with non-cancer pain
- Clinical studies
  - Two 12 week, randomized, double-blind, placebo-controlled, multicenter studies (NCT01993940 and NCT01965158)
  - 1,095 patients with OIC and non-malignant chronic pain
  - Naldemedine 0.2 mg vs. placebo

Naldemedine OIC Studies

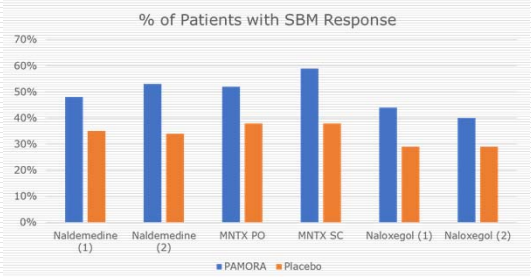


Primary efficacy: ≥3 SBMs/week with an increase of 1 or more SBM/week for at least 9 out of 12 weeks and 3 of last 4 weeks

PAMORA OIC Studies

- Methylnaltrexone study 1:
  - 4-week study comparing MNTX 450 mg PO daily to placebo (N=401)
  - Responders (patient with 3 or more SBMs/week with an increase of 1 or more SBM/week over baseline, for 3 or more out of the first 4 weeks)
- Methylnaltrexone study 2:
  - 4-week study comparing MNTX 12 mg SC daily to placebo (N=312)
  - Responders (patient with 3 or more SBMs/week for each of the 4 weeks)
- Naloxegol studies:
  - Two 12-week studies comparing naloxegol 12.5 or 25 mg daily to placebo (N=1,337)
  - Responders (≥3 SBMs/week with an increase of 1 or more SBM/week for at least 9 out of 12 weeks and 3 of last 4 weeks)

PAMORA OIC Studies



Dosing and Administration

- Dosage form/strength:
  - 0.2 mg tablets
- Dose:
  - Oral: 0.2 mg once daily with or without food
  - Alteration of analgesic dosing regimen prior to initiating naldemedine is not required
  - Patients receiving opioids for <4 weeks may be less responsive to naldemedine
  - Discontinue naldemedine is treatment with the opioid pain medication is also discontinued
  - No dosage adjustments provided

Pharmacokinetics

Parameter	Value
Bioavailability	Data not provided
Tmax	0.75 hrs
Protein Binding (VoD)	93% (155 L)
Food effect	Not significant
Metabolism	Primarily CYP3A with minor UGT1A3
Elimination half-life	11 hrs

Contraindications/Warnings/ Precautions

- Contraindications
  - Patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction
  - Patients with a history of hypersensitivity reaction to naldemedine
- Warnings and precautions
  - Gastrointestinal perforation
  - Opioid withdrawal

Adverse Reactions

- Common reactions
  - Abdominal pain
  - Diarrhea
  - Nausea
- Less common reactions
  - Gastroenteritis
  - Vomiting

Drug Interactions

- Strong CYP3A4 inducers
  - Significant decrease in naldemedine concentrations
  - Avoid concomitant use
- Other opioid antagonists
  - Potential for additive effect
  - Avoid concomitant use
- Moderate and strong CYP3A inhibitors
  - Increase in naldemedine concentrations
  - Monitor for potential naldemedine ARs
- P-glycoprotein inhibitors
  - Increase in naldemedine concentrations
  - Monitor for potential naldemedine ARs

Schedule II Controlled Substance

- Naldemedine pharmacology/toxicology
  - Opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors
  - Single doses up to 100 mg and multiple doses up to 30 mg for 10 days in healthy subjects (GI-related ARs)
- Controlled Substances Act provision that places all derivatives of opium and opioids into Schedule II
  - FDA review concluded that based on nonclinical and clinical abuse-related data, naldemedine does not have abuse potential
  - 6/8/16: DEA received petition from drug sponsor
  - 3/22/17: HHS provided DEA a scientific and medical evaluation (8 factor analysis)—DEA conducted its own 8 factor analysis
  - 7/12/17: Federal Register notice of proposed rulemaking to remove naldemedine from control

Naloxegol Timeline

- Naloxegol (Movantik®) is a pegylated derivative of naloxone
- 3/22/12: DEA received petition from drug sponsor
- 2/7/13: DEA forwarded petition to HHS
- 8/8/14: HHS provided DEA a scientific and medical evaluation (8 factor analysis)—DEA conducted its own 8 factor analysis
- 9/16/14: Naloxegol (Movantik®) FDA approved
- 10/29/14: Federal Register notice of proposed rulemaking to remove naloxegol from control
- 1/23/15: naloxegol removed from controlled status

Available at: https://www.federalregister.gov/documents/2015/01/23/2015-01172/schedules-of-controlled-substances-removal-of-naloxegol-from-control. Accessed September 2017.

Patient Counseling

- Discontinue Symproic if treatment with the opioid is also discontinued.
- Promptly seek medical attention if they develop unusually severe, persistent or worsening abdominal pain.
- Potential for opioid withdrawal symptoms.
- Should tell physicians if they are pregnant or plan to become pregnant or are breastfeeding.
- Take once daily with or without food.
- Proper storage (i.e., 68°F to 77°F).

Question #1

Abuse-deterrent opioids approved by the FDA include which of the following?

a. Hysingla ER
b. MorphaBond ER
c. OxyContin
d. RoxyBond IR
e. All of the above

Answer: e. All of the above

Question #2

Adalimumab-adbm (Cyltezo®) by Boehringer Ingelheim recently received FDA approval as being biosimilar to Humira.

a. True
b. False

Answer: a. True

Question #3

Delafloxacin (Baxdela®) received FDA approval for the treatment of community acquired bacterial pneumonia.

a. True
b. False

Answer: b. False

Question #4

Which of the following is true for betrixaban (Bevyxxa®)?

a. FDA approved for DVT prophylaxis following knee/hip replacement.
b. Initial dosing is 160 mg followed by 80 mg once daily (taken at same time each day with food).
c. Undergoes extensive CYP3A4 metabolism.
d. Package labeling does not contain black box warning regarding spinal/epidural hematoma.
e. All of the above

Answer: b. Initial dosing is 160 mg followed by 80 mg daily.

Question #5

Plecanatide (Trulance®) and naldemedine (Symproic®) are both approved for opioid-induced constipation.

a. True
b. False

Answer: b. False

Questions?