NEW DRUG UPDATES
2014
Elizabeth Cobb, Pharm.D.
Assistant Director Clinical Pharmacy Services
PGY-1 Residency Program Director
Mount Sinai Beth Israel

Disclosure
• Nothing to disclose

Objectives
• Describe the FDA approved indications for select new
drug approvals of 2014
• Review dosing, mechanism of action, route of
administration, cost and dosage forms for the new drugs
reviewed
• Discuss warnings, precautions, side effects and potential
drug interactions for these medications
• Compare and contrast the role of these new medications
with medications currently available
Who is attending this presentation?
A. Student
B. PGY-1 or PGY-2 Resident
C. Hospital Pharmacist
D. Community Pharmacist
E. Clinical Specialist
F. Director of Pharmacy/ Administrator
G. Other

How many novel new drugs were approved by the CDER in 2014?
A. 8
B. 17
C. 29
D. 41
E. 50

Overview of Approvals

- About 41% of the novel new drugs approved in 2014 (17 of 41) are First-in-Class
- Additionally 41% of the novel new drugs approved in 2014 (17 of 41) were approved to treat rare or "orphan" diseases that affect 200,000 or fewer Americans
- Demonstrates innovative nature of 2014 approvals

Fast Track

- Categorized as drugs with the potential to address unmet medical needs
- Seventeen of the 2014 novel new drugs (41%) were designated by CDER as Fast Track
- Increased levels of communication FDA allocates to drug developers and CDER reviews portions of a drug application ahead of the submission of the complete application
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**Breakthrough**
- Categorized as drugs with preliminary clinical evidence demonstrating that the drug may result in substantial improvement on at least one clinically significant endpoint (i.e., study result) over other available therapies.
- Nine of the 2014 novel new drugs (22%) designated as Breakthrough therapies.
- Includes all of the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program.

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**Priority Review**
- Categorized as drugs that potentially provide a significant advance in medical care.
- Twenty-five of the 2014 novel new drugs (61%) were designated Priority Review.
- CDER determined and set a target to review the drug within 6 months instead of the standard 10 months.

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**Accelerated Approval**
- Categorized as a drug for a serious or life-threatening illness that offers a benefit over current treatments.
- CDER approved eight of the 2014 novel new drugs (20%) under FDA's Accelerated Approval program.
- Approval is based on a “surrogate endpoint” (e.g., a laboratory measure) or other clinical measure that is considered reasonably likely to predict a clinical benefit of the drug.
- The drug must undergo additional testing to confirm that benefit after approval.
Qualified Infectious Disease Product (QIDP)

- The Generating Antibiotics Incentives Now Act (GAIN Act) provides incentives to help bring new antibiotics and other antimicrobials to market
- A drug with particular promise can be designated as a Qualified Infectious Disease Product (QIDP) by authority of the GAIN Act
- In 2014, CDER approved four new antibiotics with this designation, the first four QIDP-designated novel new drugs approved by FDA

Infectious Diseases

- Dalbavancin (Dalvance)*
- Oritavancin (Orbactiv)*
- Tedizolid (Sivextro)*
- Ceftolozane/tazobactam (Zerbaxa)*
- Tavaborole (Kerydin)
- Efinaconazole (Jublia)

*QIDP

Dalbavancin (Dalvance™)
Dalbavancin

- **FDA Indication**
  - Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following grammpositive microorganisms: Staphylococcus aureus (including MSSA and MRSA), Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus anginosus (including Streptococcus intermedius, and Streptococcus constellatus).

- **MOA**
  - Lipoglycopeptide which binds to the D-alanyl-D-alanine terminus of the stem pentapeptide in the bacterial cell wall peptidoglycan and prevents cross-linking which interferes with cell wall synthesis.
  - It is bactericidal in vitro against Staphylococcus aureus and Streptococcus pyogenes.

- **Dosing**
  - 1000 mg IVPB as a single dose initially, followed by 500 mg IVPB as a single dose 1 week later.
  - Cost: $1,788 per 500mg vial ($5,364 per patient course of therapy).

- **Contraindications**
  - Hypersensitivity to dalbavancin or to any component of the formulation.

- **Drug Interactions**
  - None reported.

- **Warnings and precautions**
  - Hypersensitivity reactions.
  - Hepatic effects.
  - Infusion reactions. Rapid intravenous infusions of dalbavancin (<30 minutes) may cause reactions that resemble “Red-Man Syndrome,” e.g., flushing of the upper body, urticaria, pruritus, rash.
  - Superinfection.
  - Adverse Effects: Nausea (5.5%), headache (4.7%), and diarrhea (4.4%) lasted for a median of 4 days and study discontinuation similar to comparator.
  - Pregnancy Category C.

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IVPB Preparation/Administration

- Reconstitute with sterile water for injection and dilute only with 5% dextrose injection to a final concentration of 1 to 5 mg/mL.
- Solution should not be co-infused with other medications or electrolytes.
- Saline-based infusion solutions may cause precipitation.
- Shared lines should be flushed before and after each dalbavancin infusion with 5% dextrose injection.
- Infuse 230 minutes to avoid infusion reaction.
- The total time from reconstitution to dilution to administration should not exceed 48 hours.
Oritavancin (Orbactiv™)

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Oritavancin

- FDA Indication
  - Treatment of adult patients with acute bacterial skin and skin-structure infections (ABSSSI) caused by or suspected to be caused by susceptible isolates of designated gram-positive microorganisms, including Staphylococcus aureus (MSSA and MRSA), Staphylococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus group (includes S. anginosus, Streptococcus intermedius, and Streptococcus constellatus), and Enterococcus faecalis (vancomycin-susceptible isolates only)
- MOA
  - Lipoglycopeptide which binds to the D-alanyl-D-alanine terminus of the peptide pentapeptide in the bacterial cell wall peptidoglycan and prevents cross-linking which interferes with cell wall synthesis
- Dosing
  - 1200mg IVPB over 3 hours single dose
- Cost
  - $1,160 per 400mg vial ($3,480 per patient single dose)


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Oritavancin

- Contraindications
  - Administration of unfractionated heparin within 48 hours due to (aPTT) test may be falsely elevated
- Drug Interactions
  - Inhibits CYP2C19 (weak), CYP2C9 (weak); Induces CYP3A4 (weak)
  - Warfarin may result in increased warfarin levels and increased risk of bleeding
- Warnings and precautions
  - Hypersensitivity
    - Infusion Reactions (pruritus, urticaria, flushing)
  - Osteomyelitis
  - Superinfection
  - Pregnancy Category C

### Slide 22

**Adverse Reactions**

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Oritavancin (n = 976)</th>
<th>Vancomycin (n = 983)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess (limb and subcutaneous)</td>
<td>3.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.7%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Fever</td>
<td>1.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.6%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

*Orbactiv (oritavancin) [prescribing information]. Parsippany, NJ: The Medicine Company; August 2014.*

### Slide 23

**IVPB Preparation/Administration**

- Reconstitute each 400 mg vial with 40 mL of SWFI and gently swirl.
- Withdraw and discard 120 mL of fluid from a D5W 1000 mL bag; withdraw 40 mL from each of 3 reconstituted vials and add to D5W to bring the total bag volume to 1000 mL (final solution concentration 1.2 mg/mL).
- Infuse slowly over 3 hours.
- If a common IV line is being used to administer other drugs in addition to oritavancin, the line should be flushed before and after each infusion with DSW.
- Reconstituted vials and diluted solution may be stored refrigerated for 12 hours or at room temperature for 6 hours.
- The total time from reconstitution and dilution to completed administration should be 58 hours at room temperature or ≤12 hours if refrigerated.

*Orbactiv (oritavancin) [prescribing information]. Parsippany, NJ: The Medicine Company; August 2014.*

### Slide 24

**Tedizolid (Sivextro™)**

*Tedizolid (Sivextro™).*
Tedizolid

- **FDA Indication**
  - Treatment of acute bacterial skin and skin structure infections (SSSIS) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including *MSSA* and *MRSA* isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* (including *S. intermedius* and *Streptococcus constellatus*), and *Enterococcus faecalis*.

- **MOA**
  - Novel, next-generation oxazolidinone prodrug rapidly converted in vivo to tedizolid.
  - Tedizolid inhibits the synthesis of bacterial proteins by interacting with the 50S subunit of bacterial ribosome, resulting in inhibition of protein synthesis.

- **Dosing**
  - 200mg IV or PO daily for 6 days.
  - Cost: $282 per 200mg vial ($1,692 per patient course).
  - $354 per 200mg tablet ($2,124 per patient course).

-Sivextro (tedizolid phosphate) [prescribing information]. Lexington, MA: Cubist Pharmaceuticals US; June 2014.

Tedizolid

- **Contraindications**
  - None listed.

- **Warnings and precautions**
  - **Superinfection**
  - **Neutropenia**

- **Adverse Effects**
  - 1% to 10%: Headache (6%), nausea (8%), diarrhea (4%), vomiting (3%), dizziness (2%), decreased platelet count (<112,000/mm3: 2%), oral candidiasis, palpitations, pseudomembranous colitis, hypertension, flushing, tachycardia, increased serum transaminases, hypersensitivity, infusion related reaction, facial paralysis, insomnia, paresthesia, pruritus, blurred vision, visual impairment, asthenopia, vitreous opacity, decreased white blood cell count, anemia, fungal infection (vulvovaginal) (<2%), peripheral neuropathy (<1%), pregnancy category C.

-Sivextro (tedizolid phosphate) [prescribing information]. Lexington, MA: Cubist Pharmaceuticals US; June 2014.

**Drug Interactions**

- Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) in vitro.

- The interaction with MAO inhibitors could not be evaluated in Phase 2 and 3 trials, as subjects taking such medications were excluded from the trials.

- **No CYP interactions expected**

- Package insert lists no interactions, Lexi Comp lists all the MAOI interactions.

-Sivextro (tedizolid phosphate) [prescribing information]. Lexington, MA: Cubist Pharmaceuticals US; June 2014.
**Slide 28**

**IVPB Preparation/ Administration**

- Each single-use vial contains lyophilized tedizolid phosphate 200 mg and must be reconstituted with 4 mL of sterile water for injection.
- The vial should be gently swirled after the addition of the sterile water for injection to completely dissolve the powder.
- The reconstituted solution is then added only to 250 mL of 0.9% sodium chloride injection; no other types of solutions should be used.
- Incompatible with any solution containing divalent cations (e.g., Ca2+, Mg2+), including Ringer’s lactate injection and Hartmann’s solution.
- IV line should be flushed before and after infusion of tedizolid with 0.9% sodium chloride injection if it will be used for sequential infusion of different drugs.

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**Ceftolozane/tazobactam (Zerbaxa™)**

- **FDA Indication**
  - Treatment of complicated intra-abdominal infections in adults, in combination with metronidazole, caused by Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Proteus mirabilis, Pseudomonas aeruginosa, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.
  - Treatment of complicated urinary tract infections, including pyelonephritis, in adults caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa.

- **MOA**
  - Combination of a cephalosporin and a beta-lactamase inhibitor.
  - Ceftolozane works by binding to penicillin-binding proteins, resulting in the inhibition of bacterial cell wall biosynthesis.

- **Dosing**
  - 1.5gm IVPB over 60 minutes every 8 hours for 4-14 days.

- **Cost**
  - $99 per 1.5g vial (1g Ceftolozane+0.5g Tazobactam).

**Slide 30**

**Ceftolozane/tazobactam**

- **FDA Indication**
  - Treatment of complicated intra-abdominal infections in adults, in combination with metronidazole, caused by Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Proteus mirabilis, Pseudomonas aeruginosa, Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius.
  - Treatment of complicated urinary tract infections, including pyelonephritis, in adults caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa.

- **MOA**
  - Combination of a cephalosporin and a beta-lactamase inhibitor.
  - Ceftolozane works by binding to penicillin-binding proteins, resulting in the inhibition of bacterial cell wall biosynthesis.

- **Dosing**
  - 1.5gm IVPB over 60 minutes every 8 hours for 4-14 days.

- **Cost**
  - $99 per 1.5g vial (1g Ceftolozane+0.5g Tazobactam).
**Ceftolozane/tazobactam**

- **Contraindications**
  - Hypersensitivity reaction to any beta-lactam, especially ceftolozane/tazobactam or piperacillin/tazobactam

- **Drug Interactions**
  - None noted

- **Warnings and precautions**
  - Hypersensitivity
  - Superinfection
  - Renal impairment

- **Adverse Effects**
  - 1% to 10%: Hypotension (<1% to 2%), atrial fibrillation (≤1%), headache (3% to 6%), insomnia (1% to 4%), anxiety (<1% to 2%), dizziness (≤1%), skin rash (≤1% to 2%), Hypokalemia (1% to 3%), nausea (3% to 8%), diarrhea (2% to 6%), constipation (2% to 4%), vomiting, abdominal pain (≤1%), anemia (<1% to 2%), thrombocythemia (<1% to 2%), increased serum ALT/AST (2%)

- **Pregnancy Category B**

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**IVPB Preparation**

- The unopened vials should be stored in a refrigerator and protected from light

- After reconstitution with sterile water for injection or sodium chloride 0.9% injection, the solution may be held for 1 hour prior to transfer and dilution in an infusion bag

- The solution is then diluted into 100 mL sodium chloride 0.9% or dextrose 5%

- The diluted solution can be stored at room temperature for 24 hours or stored in a refrigerator for up to 7 days

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**Tavaborole (Kerydin™)**
**Tavaborole**

- **FDA Indication**
  - Treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*
- **MOA**
  - Oxaborole antifungal that inhibits fungal protein synthesis by inhibition of an aminoacyl-transfer ribonucleic acid (tRNA) synthetase (AARS)
- **Dosing**
  - Topical solution applied to the affected toenails once daily for 48 weeks, using the supplied dropper
  - The solution should be applied to the toenail surface and under the tip of each toenail being treated
- **Cost**
  - $590 per 4ml bottle

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**Tavaborole**

- **Contraindications/ Drug Interactions**
  - None listed
- **Warnings and precautions**
  - None listed
  - Topical solution contains alcohol and is flammable; patients should be advised to avoid use near heat or open flame
- **Adverse Effects**
  - Incidence at least 1% and more common with active therapy than vehicle control observed in clinical trials: application-site exfoliation (2.7%), ingrown toenail (2.5%), application-site erythema (1.6%), and application-site dermatitis (1.3%)
- **Pregnancy Category C**

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**Summary/ Place in Therapy**

- Cure rates greater than those observed with ciclopirox nail lacquer
- Cure rates lower than those observed with topical efinaconazole and oral terbinafine, although head-to-head studies have not been conducted
- Not associated with the clinically important adverse effects or drug interactions that have been associated with the oral therapies
- Does not require routine liver function testing
- Therapy must be continued for 48 weeks rather than 3 to 4 months
Efinaconazole (Jublia®)

**FDA Indication**
- Treatment of onychomycosis of the toenails due to Trichophyton rubrum and Trichophyton mentagrophytes

**Mechanism of Action (MOA)**
- A topical azole antifungal; inhibits fungal lanosterol 14α-demethylase involved in the biosynthesis of ergosterol, a constituent of fungal cell membranes, resulting in fungal cell death

**Dosing**
- Topical solution should be applied to the affected toenails once daily for 48 weeks using the supplied flow-through brush applicator
- Completely cover the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate
- Wait at least 10 minutes after showering, bathing, or washing

**Cost**
- $539 per 4ml bottle

**Contraindications/ Drug Interactions**
- None listed

**Warnings and precautions**
- None listed
- Topical solution contains alcohol and is flammable; patients should be advised to avoid use near heat or open flame

**Adverse Effects**
- Incidence at least 1% and more common with active therapy than vehicle control observed in clinical trials: ingrown toenail (2.3%), application-site dermatitis (2.2%), application-site vesicles (1.6%), and application-site pain (1.1%)

**Pregnancy Category**
- C
Summary/Place in Therapy

- Cure rates greater than those observed with the ciclopirox nail lacquer or tavaborole topical solution
- Cure rates similar to those reported with oral itraconazole and terbinafine, although head-to-head studies have not been conducted
- Not associated with the clinically important adverse effects or drug interactions that have been associated with the oral therapies
- Does not require routine liver function testing
- Therapy must be continued for 48 weeks rather than 3 to 4 months with some oral agents


Onychomycosis Therapy Cost

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosage Form</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclopirox</td>
<td>Nail lacquer/topical</td>
<td>$60 per 6.6mL generic</td>
</tr>
<tr>
<td>Efinaconazole</td>
<td>Topical solution/topical</td>
<td>$59 per 4ml bottle</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Oral suspension/topical</td>
<td>$14 per 375 mg tablets</td>
</tr>
<tr>
<td>(ultramicrosize)</td>
<td></td>
<td>($450 per 30 days of therapy)</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Capsules/oral</td>
<td>$8 per 100mg capsule</td>
</tr>
<tr>
<td>(ultramicrosize)</td>
<td></td>
<td>($278 per 30 days of therapy)</td>
</tr>
<tr>
<td>Tavaborole</td>
<td>Topical solution/topical</td>
<td>$550 per 4ml bottle</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Tablets/oral</td>
<td>$13 per 250mg tablet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>($350 per 30 days of therapy)</td>
</tr>
</tbody>
</table>

Diabetes

- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
Albiglutide (Tanzeum™)

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- **Albiglutide**
- **FDA Indication**
  - Adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **MOA**
  - Glucagon-like peptide 1 (GLP-1) receptor agonist
  - Augments glucose-dependent insulin secretion and slows gastric emptying resulting in a reduction in fasting glucose and postprandial glucose
- **Dosing**
  - SubQ: 30 mg once weekly; may increase to 50 mg once weekly if inadequate glycemic response
- **Cost**
  - $97.79 per 30mg single injection pen (requires mixing)

Tanzeum (albiglutide) [prescribing information]. Wilmington, DE: GlaxoSmithKline; April 2014.

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- **Albiglutide**
- **Contraindications**
  - Severe hypersensitivity to albiglutide or any component of the formulation; history of or family history of medullary thyroid carcinoma (MTC); patients with multiple endocrine neoplasia syndrome type 2 (MEN2)
- **Adverse Effects**
  - Upper respiratory tract infection (14.2%), diarrhea (13.1%), nausea (11.1%), and injection-site reaction (10.5%)
  - Nausea and vomiting decreased in frequency over time following repeated weekly administrations
- **Pregnancy Category C**

Tanzeum (albiglutide) [prescribing information]. Wilmington, DE: GlaxoSmithKline; April 2014.
Warnings and Precautions

- Hypersensitivity reactions
- Acute pancreatitis
- Black Boxed Warning: Thyroid C-cell tumors have developed in animal studies with glucagon-like peptide-1 (GLP-1) receptor agonists; it is not known if albiglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans
- Preexisting severe gastrointestinal disease
- Renal impairment
- Concomitant use of insulin may increase the risk of hypoglycemia
- Concomitant use of an insulin secretagogue (eg, sulfonylurea) may increase the risk of hypoglycemia
- Use with caution in patients receiving medications with a narrow therapeutic window or that require rapid absorption from the GI tract due to effect on gastric emptying

Dulaglutide (Trulicity™)

- FDA Indication
  - Adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- MOA
  - Glucagon-like peptide 1 (GLP-1) receptor agonist
  - Augments glucose-dependent insulin secretion and slows gastric emptying resulting in a reduction in fasting glucose and postprandial glucose
- Dosing
  - SubQ: 0.75 mg once weekly, may increase to 1.5 mg once weekly if inadequate glycemic response; maximum: 1.5 mg once weekly
- Cost
  - $147 per 1.5mg single dose ready to use pen
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**Dulaglutide**
- **Contraindications**
  - Serious hypersensitivity to dulaglutide or any component of the formulation, personal or family history of medullary thyroid carcinoma (MTC), patients with multiple endocrine neoplasia syndrome type 2 (MEN2)
  - Adverse Effects (> 10% pts)
    - Gastrointestinal: Nausea (12% to 21%), diarrhea (9% to 13%), vomiting (6% to 13%), abdominal pain (7% to 10%)
  - Pregnancy Category C

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**Warnings and Precautions**
- Hypersensitivity reactions
- Acute pancreatitis
- Black Boxed Warning: Thyroid C-cell tumors have developed in animal studies with glucagon-like peptide-1 (GLP-1) receptor agonists; it is not known if dulaglutide causes thyroid C-cell tumor, including medullary thyroid carcinoma (MTC) in humans
- Concomitant use of an insulin secretagogue (eg, sulfonylurea) may increase the risk of hypoglycemia
- Use with caution in patients receiving medications with a narrow therapeutic window or that require rapid absorption from the GI tract due to effect on gastric emptying

**Slide 51:**

**GLP-1 agonists**

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>Albiglutide (Tanzeum)</th>
<th>Dulaglutide (Trulicity)</th>
<th>Liraglutide (Victoza)</th>
<th>Exenatide (Byetta)</th>
<th>Exenatide XR (Bydureon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Indication</td>
<td>Adjunct to diet and exercise in patients with type 2 diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C Reduction</td>
<td>~1%</td>
<td>~1.5%</td>
<td>~1%</td>
<td>~1.5%</td>
<td>~1.5%</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>~1kg</td>
<td>~2kg</td>
<td>~2kg</td>
<td>~2.5kg</td>
<td>~2.5kg</td>
</tr>
<tr>
<td>Cost/Month</td>
<td>~$330</td>
<td>~$600</td>
<td>~$450</td>
<td>~$490</td>
<td>~$410</td>
</tr>
<tr>
<td>REMS</td>
<td>Communication Plan for Acute Pancreatitis and MTC</td>
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<td></td>
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</tbody>
</table>
### Slide 52

**GLP-1 agonists**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Rate of Nausea</th>
<th>Injection Site</th>
<th>Warfarin Drug Interactions</th>
<th>Renal Use</th>
<th>Hepatic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide (Tanzeum)</td>
<td>11.1%</td>
<td>12.4%</td>
<td>None</td>
<td>No dose adjustment, use caution</td>
<td>No dose adjustment, use caution</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity)</td>
<td>12.4%</td>
<td>-</td>
<td>May increase INR</td>
<td>No dose adjustment, use caution</td>
<td>No dose adjustment, use caution</td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>8%</td>
<td>12.7%</td>
<td>None</td>
<td>No dose adjustment, use caution</td>
<td>No dose adjustment, use caution</td>
</tr>
<tr>
<td>Exenatide XR (Bydureon)</td>
<td>-</td>
<td>17.1%</td>
<td>None</td>
<td>No dose adjustment, use caution</td>
<td>No dose adjustment, use caution</td>
</tr>
<tr>
<td>Liraglutide (Victoza)</td>
<td>-</td>
<td>2%</td>
<td>None</td>
<td>No dose adjustment, use caution</td>
<td>No dose adjustment, use caution</td>
</tr>
</tbody>
</table>

### Slide 53

**SLGT2 Inhibitors**

### Slide 54

**SGLT2 Inhibitors**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
<th>Dapagliflozin</th>
<th>Manufacturer</th>
<th>Availability</th>
<th>Cost</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga</td>
<td>-</td>
<td>-</td>
<td>$12.48 per 5mg or 10mg tab</td>
<td>AstraZeneca</td>
<td>5mg, 10mg tabs</td>
<td>$12.48 per 5mg or 10mg tab</td>
<td>Inhibits sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubules, reducing reabsorption of filtered glucose from the tubular lumen and lowering the renal threshold for glucose (RTG). Results in increased urinary excretion of glucose, thereby reducing plasma glucose concentrations.</td>
</tr>
<tr>
<td>Jardiance</td>
<td>-</td>
<td>-</td>
<td>$12.03 per 10mg or 25mg tab</td>
<td>Boehringer Ingelheim</td>
<td>10mg, 25mg tabs</td>
<td>$12.03 per 10mg or 25mg tab</td>
<td></td>
</tr>
<tr>
<td>Invokana</td>
<td>-</td>
<td>-</td>
<td>$12.48 per 100mg or 300mg tab</td>
<td>Janssen</td>
<td>100mg, 300mg tabs</td>
<td>$12.48 per 100mg or 300mg tab</td>
<td></td>
</tr>
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</table>
### Slide 55

<table>
<thead>
<tr>
<th>SGLT2 Inhibitors</th>
<th>Dapagliflozin</th>
<th>Empagliflozin</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>78%</td>
<td>N/A</td>
<td>65%</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>91%</td>
<td>86.2%</td>
<td>99%</td>
</tr>
<tr>
<td>Food Effect</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Glucuronidation (minimal 3A4)</td>
<td>Glucuronidation (minimal 3A4)</td>
<td>Glucuronidation (minimal 3A4)</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>12.9 hours</td>
<td>12.4 hours</td>
<td>10.6 - 13.1 hours</td>
</tr>
<tr>
<td>Usual Adult Dosage</td>
<td>5mg once daily in the AM with or w/o food (max: 10mg/day)</td>
<td>10mg once daily in the AM with or w/o food (max: 25mg/day)</td>
<td>100mg once daily in the AM before 1st meal (max: 300mg/day)</td>
</tr>
<tr>
<td>Dosage in renal impairment</td>
<td>Do not initiate/continue if eGFR &lt;60 mL/min/1.73m²</td>
<td>Do not initiate/continue if eGFR &lt;60 mL/min/1.73m²</td>
<td>Do not initiate/continue if eGFR &lt;45 mL/min/1.73m²</td>
</tr>
</tbody>
</table>

### Slide 56

**Dapagliflozin (Farxiga™)**

- **Warnings and Precautions**
  - General mycotic infections
  - Hematologic effects: An increase in mean hemoglobin/hematocrit was observed in clinical trials
  - Hypersensitivity reactions
  - Hypotension: May cause symptomatic hypotension due to intravascular volume depletion
  - Lipid abnormality: May cause LDL cholesterol (C) elevation
  - Renal effects
  - Bladder cancer
  - Should not be used in patients with diabetic ketoacidosis (DKA)
  - Hepatic impairment
  - Should not be used in patients with type 1 diabetes mellitus (insulin-dependent, IDDM)
  - Pregnancy Category C

### Slide 57

**Dapagliflozin**

- Warnings and Precautions
  - General mycotic infections
  - Hematologic effects: An increase in mean hemoglobin/hematocrit was observed in clinical trials
  - Hypersensitivity reactions
  - Hypotension: May cause symptomatic hypotension due to intravascular volume depletion
  - Lipid abnormality: May cause LDL cholesterol (C) elevation
  - Renal effects
  - Bladder cancer
  - Should not be used in patients with diabetic ketoacidosis (DKA)
  - Hepatic impairment
  - Should not be used in patients with type 1 diabetes mellitus (insulin-dependent, IDDM)
  - Pregnancy Category C
Empagliflozin (Jardiance®)

Warnings and Precautions
- Genital mycotic infections
- Hypotension
- Lipid abnormality
- Renal effects
- Urinary tract infection
- Should not be used in patients with DKA
- Should not be used in patients with type 1 diabetes mellitus (insulin-dependent, IDDM)
- Pregnancy Category C

Miscellaneous
- Tasimelteon (Hetlioz)
- Suvorexant (Belsomra)
- Naloxegol (Movantik)
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Tasimelteon (Hetlioz™)

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Tasimelteon

- FDA Indication
  - Treatment of non-24-hour sleep-wake disorder (Non-24), a condition affecting blind individuals without light perception
- MOA
  - Agonist of melatonin receptors MT₁ and MT₂ (greater affinity for the MT₂ receptor than the MT₁ receptor). Agonism of MT₁ is thought to preferentially induce sleepiness, while MT₂ receptor activation preferentially influences regulation of circadian rhythms
- Dosing
  - 20 mg by mouth each night, 1 hour before bedtime, at the same time every night
  - Capsules should be swallowed whole and taken without food
  - Beneficial effects may not occur for weeks to months depending on the patient's circadian rhythm
- Cost
  - $281 per 20mg capsule

Hetlioz (tasimelteon) [prescribing information]. Washington, DC: Vanda Pharmaceuticals; January 2014.

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Tasimelteon

- Contraindications
  - None listed
- Warnings and precautions
  - CNS depression
  - Hepatic impairment
  - Use with caution in the elderly
  - Smokers: Smoking causes induction of CYP1A2 levels; tasimelteon exposure is decreased in smokers compared to non-smokers
- Adverse Effects
  - The most common adverse reactions reported in clinical trials occurring in at least 5% of patients and twice as often with tasimelteon than with placebo include headache, increased ALT, nightmares, vivid or unusual dreams, upper respiratory tract infection, and urinary tract infection
- Pregnancy Category
  - C

Hetlioz (tasimelteon) [prescribing information]. Washington, DC: Vanda Pharmaceuticals; January 2014.
Drug Interactions

- **Strong CYP1A2 inhibitors** (e.g., fluvoxamine) can significantly increase the exposure of tasimelteon

- **Moderate CYP1A2 inducers** (e.g., smoking) decrease the exposure of tasimelteon by approximately 40%

- **Strong inducers of CYP3A4** (e.g., rifampin) can significantly reduce systemic exposure to tasimelteon

- **Strong CYP3A4 inhibitors** (e.g., ketoconazole) increase the exposure of tasimelteon by approximately 54%. This increase was not considered clinically relevant, and no dosage adjustment is required.

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Suvorexant (Belsomra®)

**FDA Indication**
- Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance

**MOA**
- A dual orexin receptor antagonist, binding the orexin-1 and orexin-2 receptors. Endogenous orexin A and B bind to the orexin receptors and are involved with the regulation of arousal and wakefulness. Suvorexant is able to block the effects of the orexin compounds and promote sleep

**Dosing**
- 10 mg once daily within 30 minutes of bedtime; may increase to a maximum of 20 mg once daily if the 10 mg dose is well tolerated but not effective. Maximum daily dose: 20 mg

**Cost**
- $10.52 per tablet (all strengths) (C-IV)
Suvorexant

- Contraindications
  - Narcolepsy

- Adverse Effects
  - Somnolence (reported in 7% of patients)
  - Other adverse effects reported in at least 2% of suvorexant-treated patients included headache (7%), dizziness (3%), and abnormal dreams, cough, diarrhea, dry mouth, and upper respiratory tract infection (2%).
  - Somnolence occurred more frequently in females than males (8% vs 3%), as did headache, abnormal dreams, dry mouth, cough, and upper respiratory tract infection.
  - Pregnancy Category C

Drug Interactions

- Caution if coadministered with other CNS depressant medications
- Avoid concurrent alcohol ingestion
- Avoid use with strong CYP3A inhibitors (eg, ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, indinavir, boceprevir, telaprevir, teadifloxacin, conivaptan)
  - Exposure is substantially reduced, potentially resulting in reduced efficacy, if administered with strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin).
- Slightly increased digoxin levels were observed because of inhibition of intestinal P-glycoprotein - monitor digoxin levels

Warnings/Precautions

- Abnormal thinking/behavioral changes
- May cause CNS depression impairing physical and mental capabilities
- Sleep paralysis (inability to move or speak for up to several minutes during sleep-wake transitions), sleepwalking, nightmares, hallucinations, and catatonia
  - An increased risk for hazardous sleep-related activities such as sleep-driving, cooking and eating food, making phone calls, or having sex while awake
  - Use with caution in patients with depression; worsening of depression, including suicide or suicidal ideation has been reported with the use of hypnotics
  - Use with caution in patients with a history of drug dependence
  - Hepatic impairment
  - Use with caution in patients with respiratory compromise, COPD, or sleep apnea
  - Exposure is increased in females compared to males
  - Exposure is increased in obese compared to non-obese patients
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**FDA-Approved Indications for Nonbenzodiazepine Hypnotics**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suvorexant</td>
<td>Treatment of insomnia characterized by difficulty with sleep onset</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td>Treatment of insomnia characterized by difficulty with sleep maintenance</td>
</tr>
<tr>
<td>Doxepin</td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>Ramelteon</td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>Zaleplon</td>
<td><strong>X</strong></td>
</tr>
<tr>
<td>Zolpidem extended release</td>
<td></td>
</tr>
<tr>
<td>Zolpidem immediate release</td>
<td></td>
</tr>
</tbody>
</table>

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**Naloxegol (Movantik™)**

- **FDA Indication**
  - Treatment of opioid-induced constipation in adult patients with chronic noncancer pain

- **MOA**
  - Mu-opioid receptor antagonist
  - Composed of naloxone conjugated with a polyethylene glycol polymer, which limits its ability to cross the blood-brain barrier
  - At the recommended dose, naloxegol functions peripherally in tissues such as the GI tract, thereby decreasing the constipation associated with opioids

- **Dosing**
  - 25 mg once daily in the morning on an empty stomach
  - Discontinue treatment if opioid pain medication is discontinued

- **Cost**
  - $7.91 per 25mg tablet (not available yet) (CII)
  - Methylnaltrexone (Relistor) $79 per dose

**Movantik (naloxegol) [prescribing information].** Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2014.

### Slide 72

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**Movantik (naloxegol) [prescribing information].** Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2014.
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**Naloxegol**

- **Contraindications**
  - Patients with a history of bowel obstruction and bowel perforation due to the risk of GI perforation
  - Coadministration with strong CYP3A4 inhibitors (eg, clarithromycin, ketoconazole); coadministration may precipitate opioid withdrawal: symptoms include hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning
  - Patients with known hypersensitivity to naloxegol or any of its excipients (eg, mannitol, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, propyl gallate, hypromellose, titanium dioxide, polyethylene glycol, von oeste red, iron oxide black)

- **Adverse Effects**
  - Abdominal pain (12% to 21%), headache (4%), hyperhidrosis (≤3%), diarrhea (6% to 9%), nausea (7% to 8%), flatulence (3% to 6%), vomiting (5%)

- **Pregnancy Category** C

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**Warnings and Precautions**

- GI perforation has been reported with use of another peripherally acting opioid antagonist (ie, methylnaltrexone) in patients with reduced wall integrity of the GI tract (eg, peptic ulcer disease, Ogilvie syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies, peritoneal metastases)
- Symptoms consistent with opioid withdrawal (eg, hyperhidrosis, chills, abdominal pain, anxiety, irritability)
- Hepatic impairment
- Renal impairment

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**Drug Interactions**

- Strong inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, clarithromycin) may lead to increased plasma levels of naloxegol. This may increase the risk of adverse events; coadministration is contraindicated
- Moderate inhibitors of CYP3A4 (eg, diltiazem, erythromycin, verapamil) may increase plasma concentrations of naloxegol and the incidence of adverse events. Coadministration of methylnaltrexone, another opioid receptor antagonist, is not recommended. Naloxegol with moderate CYP3A4 inhibitors should be avoided; if unavoidable, reduce the daily dose to 12.5 mg and monitor for adverse reactions
- Strong inducers of CYP3A4 (eg, rifampin, carbamazepine, St. John’s wort) reduce the efficacy of naloxegol; use is not recommended
- Coadministration with other opioid receptor antagonists (eg, alvimopan, naloxone, nalbuphine, methylnaltrexone) may potentiate the risk of opioid withdrawal and is not recommended
- Naloxegol is a substrate of P-gp. Concurrent use of naloxegol with P-gp inhibitors may precipitate opioid withdrawal
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**Place in Therapy**

- Advantages over other available medications include oral administration and once-daily dosing
- Patients previously not responding to laxatives showed similar responses to the pooled results for all the naloxegol-treated patients in the studies
- Head-to-head comparisons with other laxatives have not been performed
- Controlled substance due to chemical structure not due to risk of dependence
- Potential cost advantage to other treatments

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**Rare Diseases Medication Approvals**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elosulfase alfa (Vimizim)</td>
<td>Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome), a rare genetic disorder resulting in skeletal deformities, growth retardation, and heart problems</td>
</tr>
<tr>
<td>Miltefosine (Impavido)</td>
<td>Rare tropical disease called leishmaniasis</td>
</tr>
<tr>
<td>Siltuximab (Sylvant)</td>
<td>Multicentric Castleman's disease (MCD), which results in excessive lymph node growth</td>
</tr>
<tr>
<td>Eliglustat (Cerdelga)</td>
<td>Gaucher disease, a rare genetic disorder resulting in an increase of the size of the liver and spleen, a low number of red blood cells, easy bruising caused by a decrease in blood platelets, lung disease, and bone problems</td>
</tr>
<tr>
<td>Elsber (Pereflavinone) and Nintedanib (Ofev)</td>
<td>Idiopathic pulmonary fibrosis, which results in decreasing lung function and breathing failure</td>
</tr>
<tr>
<td>Metreleptin (Myalept)</td>
<td>Complications of lipodystrophy associated with a deficiency of the hormone leptin</td>
</tr>
</tbody>
</table>

2014 CDER Update

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**Which of the following was approved in 2014 using the QIDP process?**

A. Naloxegol  
B. Efinaconazole  
C. Dalbavancin  
D. Albiglutide
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Which of the following antibiotics only requires a single dose for treatment?

A. Ceftolozane/Tazobactam
B. Dalbavancin
C. Oritavancin
D. Tedizolid

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Which of the following medications is an oral therapy used for opioid-induced constipation in adult patients with chronic noncancer pain?

A. Methylnaltrexone
B. Suvorexant
C. Tasimelteon
D. Naloxegol

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Questions?