New Drug Review Fall 2014

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Disclosure

- I do not have any conflict of interest or relevant financial relationship to report.

Objectives

- List the indications, pharmacological categories, dosage forms, drug interactions contraindications/warnings, and most common side effects of some of the newest drugs and biologics approved for use in the United States.
- Describe in greater detail the pharmacology of recently approved drugs and biologics that possess a novel mechanism of action.
- Recognize important new formulations and/or indications for previously approved drugs and biologics.

STEPS

Am Fam Physician. 2010;82(1):53-57.

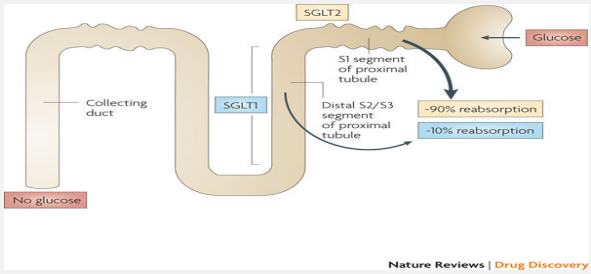
- A mnemonic to provide an analytic framework for making better decisions about a new drug's appropriate place in therapy.
- New drugs are often less tested and have very little published safety & efficacy data
- S = Safety
- T = Tolerability
- E = Efficacy
- P = Price
- S = Simplicity

Farxiga® (dapagliflozin)

- Category
  - Sodium-glucose cotransporter-2 (SGLT2) inhibitor
- Indication
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM)
  - NOT indicated for type 1 DM

Mechanism of Action

dapagliflozin



http://www.nature.com/nrd/journal/v9/n7/fig_tab/nrd3180_F3.html

Safety

dapagliflozin

- Contraindicated in severe renal impairment, end-stage renal disease, or dialysis
  - Do not use if eGFR is below 60 ml/min/1.73 m^2
  - Increases serum creatinine & decreases eGFR
- Hypotension
  - Due to intravascular volume contraction (osmotic diuresis)
  - Assess volume status before use and correct hypovolemia
  - Patient at increased risk
    - Elderly
    - Renal dysfunction
    - Use of loop diuretics

Safety

dapagliflozin

- Hypoglycemia
  - when combined with insulin or insulin secretagogue
- Genital mycotic infections
- Increases LDL-C
- Bladder cancer
  - 10 cases (0.17%) vs. 1 case (0.03%) – insufficient data
  - Do not use in patients with bladder cancer

Tolerability

dapagliflozin

Most common adverse reactions

- Female genital mycotic infections
- Nasopharyngitis
- Urinary tract infections

Other adverse reactions

- Increased urination
- Male genital mycotic infections
- Dyslipidemia
- Constipation
- Discomfort with urination
- Nausea
- Volume depletion

dapagliflozin

Efficacy

Diabetes Metab Res Rev 2014; 30: 204-221.

- Meta-analysis of 10 randomized controlled trials (RCTs) to assess efficacy and safety of dapagliflozin treatment
- 3,464 treated with dapagliflozin; 1,331 in control groups
- 308 trials initially identified
  - Exclusion reasons included not RCTs, did not describe dapagliflozin treatment, and durations < 12 weeks

	Weighted mean difference	95% confidence interval (CI)	P-value
HbA_{1c}	-0.53%	-0.58% to -0.47%	<0.00001
Fasting plasma glucose	-1.06 mmol/L (19 mg/dl)	-1.20 to -0.92 mmol/L	<0.00001
Body weight	-1.63 kg	-1.83 to -1.43 kg	<0.00001

Efficacy

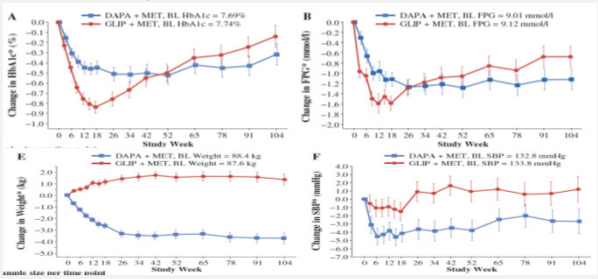
Diabetes, Obesity and Metabolism 2014. Published online July 2014.
DOI: 10.1111/dom.12327

- 52 week, randomized, double blind study with 52-week double-blind extension period
- Dapagliflozin (n=406) vs. glipizide (n=408)
- All patients were on metformin ≥ 1500 mg/d
- Baseline HbA_{1c} 6.5-10%
- Patients with inadequate response at max dose were discontinued from the study
- Primary endpoint - HbA_{1c} non-inferiority
- Secondary endpoints - change in body weight
- Only ½ of the study participants completed 104 weeks

dapagliflozin

Efficacy

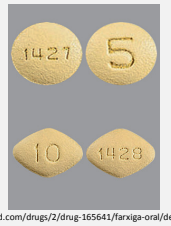
Diabetes, Obesity and Metabolism 2014. Published online July 2014



dapagliflozin

Price

- How Supplied – 5 and 10 mg tablets
- AWP
  - $12.48 each
  - $374.40 per 30-day supply
- Comparators
  - Invokana® (canagliflozin) - $12.48 ea. ($374.40 per 30-d)
  - Jardiance® (empagliflozin) - $12.04 ea. ($361.20 per 30-d)



http://www.webmd.com/drugs/2/drug-165641/farxiga-oral/details#images

dapagliflozin

Simplicity

dapagliflozin

- Starting Dose – 5 mg once daily
  - Take in the morning
  - With or without food
- Dose can be increased to 10 mg once daily in patients tolerating the drug who need additional glycemic control
- Assess renal function prior to starting
- No dose adjustments needed in the elderly

Jardiance® (empagliflozin)

- Category
  - Sodium-glucose cotransporter-2 (SGLT2) inhibitor
- Indication
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM)
  - NOT indicated for type 1 DM

Safety

empagliflozin

- Contraindicated in severe renal impairment, end-stage renal disease, or dialysis
  - Do not use if eGFR is below 45 ml/min/1.73 m^2
  - Increases serum creatinine & decreases eGFR
- Hypotension
  - Due to intravascular volume contraction (osmotic diuresis)
  - Assess volume status before use and correct hypovolemia
  - Patient at increased risk
    - Elderly
    - Renal dysfunction
    - Use of diuretics

Safety

empagliflozin

- Hypoglycemia
  - when combined with insulin or insulin secretagogue
- Genital mycotic infections
- Urinary tract infections
- Increases LDL-C

Tolerability

empagliflozin

Most common adverse reactions

- Female genital mycotic infections
- Urinary tract infections

Drug Interactions

- Diuretics
- Insulin or insulin secretagogues

Other adverse reactions

- Upper respiratory tract infection
- Increased urination
- Male genital mycotic infections
- Dyslipidemia
- Nausea
- Volume depletion

Efficacy

Drugs in Context 2014; 3: 212262

Table 3. Results in empagliflozin Phase III clinical trials.

Patients Background therapy Planned enrollment (n)	Study duration	Treatment arms	Primary endpoint
Monotherapy			Change from baseline in HbA1c, mean (95% CI)
NCT01177813 [58] Adults with type 2 diabetes Drug naïve n=986	24 weeks	Empagliflozin 10 mg qd Empagliflozin 25 mg qd Sitagliptin 100 mg qd Placebo Open-label empagliflozin 25 mg qd[a]	−0.66% (−0.76, −0.56) −0.78% (−0.88, −0.67) −0.66% (−0.76, −0.56) +0.08% (−0.03, +0.18) −3.70% (−4.11, −3.29)
Add-on therapy			Change from baseline in HbA1c, mean ± SE
NCT01210001 [62] Adults with type 2 diabetes Pioglitazone ± metformin n=499	24 weeks	Empagliflozin 10 mg qd Empagliflozin 25 mg qd Placebo	−0.59 ± 0.07% −0.72 ± 0.07% −0.11 ± 0.07%
NCT01159600-met [60] Adults with type 2 diabetes Metformin n=637	24 weeks	Empagliflozin 10 mg qd Empagliflozin 25 mg qd Placebo Open-label empagliflozin 25 mg qd[a]	−0.70 ± 0.05% −0.77 ± 0.05% −0.13 ± 0.05% −3.23 ± 0.23%
NCT01159600 [61] Adults with type 2 diabetes Metformin + sulfonylurea n=669	24 weeks	Empagliflozin 10 mg qd Empagliflozin 25 mg qd Placebo Open-label empagliflozin 25 mg qd[a]	−0.82 ± 0.05% −0.77 ± 0.05% −0.17 ± 0.05% −2.89 ± 0.16%
Special populations			Co-primary endpoints: change from baseline in HbA1c, mean ± SE and 24-hour SBP, mean ± SE
NCT01370005 [64] Adults with type 2 diabetes & hypertension n=825	12 weeks	Empagliflozin 10 mg qd Empagliflozin 25 mg qd Placebo	HbA1c: −0.59 ± 0.04 24-hour SBP: −2.95 ± 0.48 HbA1c: −0.62 ± 0.04 24-hour SBP: −1.68 ± 0.48 HbA1c: +0.03 ±0.04 24-hour SBP: +0.48 ± 0.49
			Change from baseline in HbA1c, mean (95% CI)
NCT01164501 [63] Adults with type 2 diabetes & renal impairment Any antidiabetic therapy n=741	52 weeks (primary endpoint after 24 weeks)	Patients with stage 2 CKD: Empagliflozin 10 mg qd Empagliflozin 25 mg qd Placebo Patients with stage 3 CKD: Empagliflozin 25 mg qd Placebo	−0.46% (−0.60, −0.32) −0.63% (−0.77, −0.49) +0.06% (−0.08, +0.20) −0.37 (−0.47, −0.27) +0.05 (−0.05, +0.15)

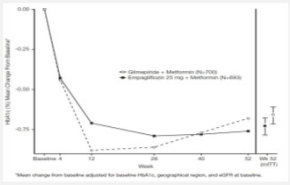
qd, once daily; SBP, systolic blood pressure.
[a]In patients with screening HbA1c >11%.
[b]Estimated glomerular filtration rate (eGFR) of <90 mL/min, as determined during screening and the run-in phase, using the Modification of Diet in Renal Disease (MDRD) equation, patients with eGFR <15 mL/min were excluded.
doi: 10.7573/dic.212262.t003

empagliflozin

Efficacy - *The Lancet Diabetes & Endocrinology* 2(9):691-700, September 2014

empagliflozin

- 104-wk, randomized, active-control, double-blind, phase 3 trial
- 1549 patients with Type 2 DM and HbA1c of 7-10% despite metformin treatment
- Randomized 1:1 to either
  - Empagliflozin 25 mg once daily (n=765)
  - Glimepiride 1-4 mg once daily (n=780)
- Primary endpoint - change in HbA1c at 52 and 104 weeks



- At week 104, adjusted mean difference in change from baseline in HbA1c with empagliflozin vs glimepiride was −0·11% (95% CI −0·19 to −0·02; p=0·0153 for superiority).

Price

- How supplied - 10 & 25 mg tablets
- AWP
  - $12.04 each
  - $361.20 per 30-day supply
- Comparators
  - Invokana® (canagliflozin) - $12.48 ea. ($374.40 per 30-d)
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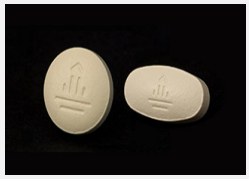


http://www.empr.com/jardiance-launched-for-type-2-diabetes/article/368076/

empagliflozin

empagliflozin

Simplicity

- Starting Dose – 10 mg once daily
  - Take in the morning
  - With or without food
- Dose can be increased to 25 mg once daily in patients tolerating the drug who need additional glycemic control
- Assess renal function prior to starting
- No dose adjustments needed in the elderly

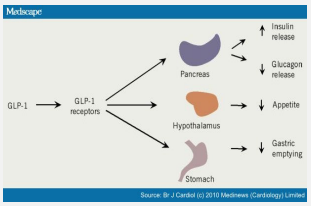
Tanzeum® (albiglutide)

- Category
  - Glucagon-like peptide-1 (GLP-1) receptor agonist
- Indication
  - An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Limitations
  - Not recommended as first-line therapy
  - Not for Type 1 DM or patients with severe GI disease
  - Has not been studied in patients with pancreatitis
  - Has not been studied in combination with prandial insulin

albiglutide

Mechanism of Action

- Recombinant fusion protein comprised of 2 tandem copies of modified human GLP-1 genetically fused in tandem to human albumin
- The GLP-1 fragment sequence 7 - 36 has been modified (glycine for alanine) at position 8 to confer resistance to DPP-IV
- The human albumin moiety together with the DPP-IV resistance, extends the half-life (5 days) allowing once-weekly dosing



http://www.medscape.com/viewarticle/751632_2

albiglutide

Safety

BLACK BOX WARNING

- Risk of thyroid C-cell tumors (Medullary Thyroid Carcinoma)
- Contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Based on rodent studies of clinically relevant doses of GLP-1 agonists
- Dose-dependent and treatment-duration-dependent
- Not known if increased risk in humans exist

albiglutide

Safety

- Acute Pancreatitis
  - 6 cases (0.3%) in clinical trials vs. 0 (placebo) / 2 (0.1%) active comparator
  - Observe for s/s, discontinue if symptomatic
  - Do not use in patients with h/o pancreatitis
- Hypoglycemia
  - Primarily when used with insulin or sulfonylurea
  - Consider empirically lowering doses
- Hypersensitivity
- Renal impairment
  - More common if suffering from n/v, diarrhea, dehydration

albiglutide

Tolerability

Most common ADRs (≥10%)

- Upper respiratory tract infection
- Diarrhea
- Nausea
- Injection site reaction
  - Hematoma, erythema, rash, pruritus, hypersensitivity

Rare ADR

- Pneumonia, atrial fibrillation, appendicitis, anti-albiglutide antibodies, LFT abnormalities

Drug Interactions

- Decreases absorption of oral medications due to delayed gastric emptying

Ann Pharmacother. 2014 Aug 18. pii: 1060028014545807. [Epub ahead of print]

Table 2. Summary of Randomized Controlled Trials of Albiglutide in T2D.

Study	Design	Patient Population	Treatment Groups	Change in A1C From Baseline (%)	Change in Weight From Baseline (kg)
Reusch et al[18] (HARMONY 1)	R, DB, PC, n = 299, 52 weeks	Inadequately controlled on pioglitazone ± metformin; mean age = 53 years; A1C = 8.1%, BMI = 34 kg/m²; duration of diabetes = 8 years	Albi 30 mg once weekly Placebo	−0.81 −0.05	+0.28 +0.45
Reinhardt et al[19] (HARMONY 2)	R, DB, PC, n = 296, 52 weeks	Drug naive, inadequately controlled on diet and exercise; mean age = 53 years; A1C = 8.1%; BMI = 34 kg/m²; duration of diabetes = 4 years	Albi 30 mg once weekly Albi 50 mg once weekly Placebo	−0.7 −0.9 +0.2	−0.4 −0.9 −0.7
Ahren et al[14] (HARMONY 3)	R, DB, PC, AC, n = 1012, 104 weeks	Inadequately controlled on metformin; mean age = 55 years; A1C = 8.1%; BMI = 32.6 kg/m²; duration of diabetes = 6 years	Albi 30-50 mg once weekly Sita 100 mg once daily Glimepiride 2-4 mg once daily Placebo	−0.63 −0.28 −0.36 +0.27	−1.21 −0.86 +1.17 −1.0
Pratley et al[16] (HARMONY 4)	R, OL, AC, NI, n = 735, 52 weeks	Inadequately controlled on metformin ± SU; mean age = 56 years; A1C = 8.3%; BMI = 33 kg/m²; duration of diabetes = 8.8 years	Albi 30-50mg once weekly Insulin glargine once daily	−0.67 −0.79	−1.05 +1.56
Stewart et al[15] (HARMONY 5)	R, DB, AC, NI, n = 685, 52 weeks	Inadequately controlled on metformin ± a glinopeptide; mean age = 55 years; A1C = 8.2%; BMI = 32.2 kg/m²; duration of diabetes = 8.9 years	Albi 30-50mg once weekly Pio 30-45mg once daily Placebo	−0.55 −0.8 +0.33	−0.4 +4.4 −0.4
Rosenstock et al[17] (HARMONY 6)	R, OL, AC, NI, n = 566, 26 weeks	Inadequately controlled on basal insulin ± metformin ± TZD; mean age = 56 years; A1C = 8.45%; weight = 92 kg; duration of diabetes = 11 years	Albi 30-50 mg once weekly Insulin lispro 3 times daily	−0.82 −0.66	−0.73 +0.81
Pratley et al[17] (HARMONY 7)	R, OL, AC, NI, n = 841, 32 weeks	Inadequately controlled on oral drugs (metformin, pioglitazone, SU, or any combination); mean age = 56 years; A1C = 8.2%; BMI = 32.8 kg/m²; duration of diabetes = 8.4 years	Albi 50 mg once weekly Lira 1.8 mg once daily	−0.78 −0.99	−0.64 −2.19
Leiter et al[13] (HARMONY 8)	R, AC, NI, n = 486, 26 weeks	Renal impairment (eGFR = 15-89 mL/min/1.73 m²) and inadequately controlled on lifestyle, metformin, TZD, SU, or any combination; mean age = 63 years; A1C = 8.2%; weight = 83 kg; duration of diabetes = 11.2 years	Albi 30-50 mg once weekly Sita once daily, dose renally adjusted	−0.83 −0.52	−0.8 −0.2

albiglutide

Price

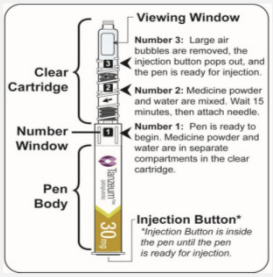
http://us.gsk.com/media/189809/Tanzeum-albiglutide-Pen-Product-Photo.jpg

- How Supplied
  - 30 & 50 mg lyophilized powder in a single dose pen
- AWP - $97.79 each ($391.16 per month)
- Comparators (AWP monthly cost)
  - Byetta® (exenatide BID) - $512-534
  - Bydureon® (exenatide once weekly) - $528.06
  - Victoza® (liraglutide once daily) - $470.88 or $706.32

albiglutide

Simplicity

- Starting dose - 30 mg SQ once weekly
- May increase to 50 mg dose if needed
- Injection sites - abdomen, thigh, upper arm
- Administer at any time of day without regard to meals
- No renal adjustment necessary
- Store refrigerated
  - Room temp for up to 4 weeks



- Use within 8 hours after reconstitution

albiglutide

Afrezza® (inhaled human insulin)

- Category
  - Rapid acting inhaled insulin
- Indication
  - To improve glycemic control in adult patients (≥18 y/o) with diabetes mellitus
- Limitations
  - Must use with long-acting insulin in Type 1 DM
  - Not recommended for treatment of DKA
  - Not recommended in patients who smoke

Mechanism of Action

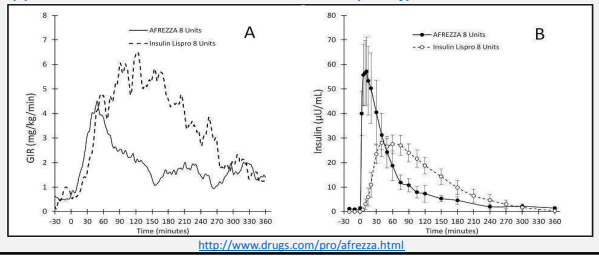
Inhaled human insulin

- Insulin lowers blood glucose levels by
  - stimulating peripheral glucose uptake by skeletal muscle and fat
  - inhibiting hepatic glucose production
  - inhibits lipolysis in adipocytes
  - inhibits proteolysis, and enhances protein synthesis.
- Technosphere insulin (TI)
  - Insulin is adsorbed onto carrier particles consisting of fumaryl diketopiperazine (FDKP) and polysorbate 80 forming microspheres.

Mechanism of Action

Inhaled human insulin

Baseline-Corrected Glucose Infusion Rate (A) and Baseline-Corrected Serum Insulin Concentrations (B) after Administration of Afrezza or Subcutaneous Insulin Lispro in Type 1 Diabetes Patients



http://www.drugs.com/pro/afrezza.html

Inhaled human insulin

Safety

BLACK BOX WARNING

- Risk of acute bronchospasm in patients with chronic lung disease
- Contraindicated in asthma or COPD
- Baseline FEV_1 required for all patients

Other contraindications

- During an episode of hypoglycemia
- Hypersensitivity to regular human insulin
  - Severe, life-threatening allergic reactions to insulin products are possible

Inhaled human insulin

Safety

- Hypoglycemia
- Decline in pulmonary function
  - small [40 mL (95% CI: -80, -1)] but greater FEV_1 decline vs comparator
  - Reassess FEV_1 at 6-months, and then annually
  - Consider discontinuing in patients with decline of ≥ 20% in FEV_1
  - Effects of using > 2 years has not been established
- Lung cancer (data insufficient)
- DKA more common (0.43%; n=13 vs 0.14%; n=3)
- Hypokalemia
- Fluid retention/Heart failure when used with thiazolidinedione

Inhaled human insulin

Tolerability

Most common ADRs (≥2%)

- Hypoglycemia
- Cough (most common reason for d/c)
- Throat pain/irritation
- Others – headache, fatigue, diarrhea, nausea, weight gain
- Drug Interactions – same as other insulin products

Inhaled human insulin

Efficacy *Lancet* 2010; 375: 2244–53

- 52-week, randomized, open-label study
- 677 adult patients with Type 2 DM with poor glycemic control on insulin therapy
- Baseline HbA_{1c} 7-11%
- Randomized 1:1 to
  - Prandial inhaled insulin + bedtime insulin glargine (n=334)
  - BID insulin aspart 70/30 mix (n=343)
- Primary Endpoint
  - Change in HbA_{1c} from baseline
  - Non-inferiority margin - 0.4% (per protocol analysis)

Inhaled human insulin

Efficacy *Lancet* 2010; 375: 2244–53

	Inhaled insulin plus insulin glargine	Biaspart insulin	Difference between inhaled insulin plus insulin glargine and biaspart insulin
Modified intention-to-treat population			
Number of patients	213	243	NA
Change in HbA_{1c}	−0·66% (0·078, −0·82 to −0·51)	−0·72% (0·071, −0·86 to −0·58)	0·06% (0·101, −0·14 to 0·25)
Modified intention-to-treat population (last observation carried forward)			
Number of patients	302	316	NA
Change in HbA_{1c}	−0·59% (0·063, −0·71 to −0·47)	−0·71% (0·061, −0·83 to −0·59)	0·12% (0·085, −0·05 to 0·29)
Per-protocol population			
Number of patients	211	237	NA
Change in HbA_{1c}	−0·68% (0·077, −0·83 to −0·53)	−0·76% (0·071, −0·90 to −0·62)	0·07% (0·102, −0·13 to 0·27)

Data are least squares mean (SE, 95% CI), and were calculated by ANCOVA. NA=not applicable.

Table 3: Change in glycosylated haemoglobin (HbA_{1c}) from baseline to week 52 by analysis population

Price

http://www.techtimes.com/articles/9398/20140630/fast-acting-inhaled-insulin-afrezza-gets-fda-nod.htm

- How supplied
  - 4 unit and 8 unit single-use cartridges for oral inhalation
  - Inhaler can be used for up to 15-days, then discard
  - 2 inhalers come in each box of 60, 90, or 180 cartridges
- Price TBD
  - MannKind Corporation finalizing partnership agreement to help market the product
  - Anticipated availability - 1st quarter 2015
  - Expected to be par-priced with rapid-acting insulin pens

Inhaled human insulin

Inhaled human insulin

Simplicity

- Insulin Naïve Individuals
  - Start on 4 units at each meal
- Titrate dose to desired effect
- Reduces # of injections/day
- Storage
  - Not in use - refrigerated
  - In use may be kept at room temp
    - 10 days unopened
    - 3 days opened

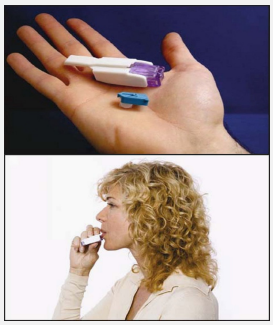
- Mealtime dose conversion table

Injected Mealtime Insulin Dose	AFREZZA® Dose	# of 4 unit (blue) cartridges needed	# of 8 unit (green) cartridges needed
up to 4 units	4 units		
5-8 units	8 units		
9-12 units	12 units		
13-16 units	16 units		
17-20 units	20 units		
21-24 units	24 units		

Inhaled human insulin

Simplicity

First inhaled insulin product - Exubera®
No longer marketed



QUESTION #1

The new diabetes medication, canagliflozin, inhibits sodium-glucose co-transporter 2 (SGLT2) resulting in

A. increased pancreatic insulin secretion.

B. increased urinary glucose excretion.

C. decreased gastrointestinal glucose absorption.

D. improved insulin sensitivity.

QUESTION #1

The new diabetes medication, canagliflozin, inhibits sodium-glucose co-transporter 2 (SGLT2) resulting in

A. increased pancreatic insulin secretion.

B. increased urinary glucose excretion.

C. decreased gastrointestinal glucose absorption.

D. improved insulin sensitivity.

QUESTION #2

Patients with this condition should not use the new inhaled insulin product, Afrezza®?

A. COPD

B. Myocardial Infarction

C. Obesity

D. Pancreatitis

QUESTION #2

Patients with this condition should not use the new inhaled insulin product, Afrezza®?

A. COPD

B. Myocardial Infarction

C. Obesity

D. Pancreatitis

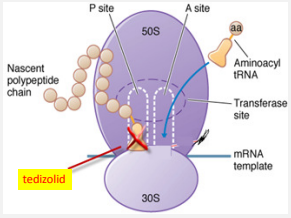
Sivextro® (tedizolid)

- Category
  - Oxazolidinone antibacterial agent
- Indication
  - Treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients caused by designated susceptible bacteria including MRSA

Mechanism of Action

tedizolid

- Inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit
- Bacteriostatic
- Spectrum of Activity
  - Primarily Gram + organisms such as *staphylococcus* (including MRSA), *streptococcus, enterococcus*
- Prodrug (tedizolid phosphate)
  - Phosphatases convert to tedizolid



http://www.antibiotics-info.org/linezolid.html

Safety

tedizolid

- Patients with neutropenia
  - Safety and efficacy not established
  - Animal studies showed activity was reduced in the absence of granulocytes
- *Clostridium difficile*-Associated Diarrhea (CDAD)
- Development of drug-resistant bacteria
  - Follow good antibiotic stewardship

Tolerability

tedizolid

Most Common ADRs (≥2%)
- Nausea
- Headache
- Diarrhea
- Vomiting
- Dizziness

Rare
- Myelosuppression
  - Appears to be less than linezolid
- Peripheral & optic neuropathy

Drug Interaction
- MAO inhibitors
- Adrenergic agents
- Serotonergic agents

- Due to weak MAO inhibition
  - Initial data show minimal effects when tedizolid is combined with these drugs
  - No tyramine food restriction needed

Efficacy – Establish-1 study

tedizolid

JAMA. 2013;309(6):559-569

- Randomized, double-blind, double-dummy, multicenter, phase 3 noninferiority trial
- 667 adult patients with ABSSSI (Gram + organism suspected or documented)
- Randomized 1:1 to receive oral treatment of
  - Tedizolid 200 mg once daily x 6 days (n=332)
  - Linezolid 600 mg BID x 10 days (n=335)
- Primary efficacy endpoint
  - Early clinical response at the 48-72 hour assessment
  - 10% noninferiority margin was predefined

Efficacy – Establish-1 study

tedizolid

JAMA. 2013;309(6):559-569

Table 2. Clinical Response at Early and Late Time Points

Clinical Response	Tedizolid Phosphate (n = 332)	Linezolid (n = 335)	Absolute Treatment Difference (95% CI), %
At the 48- to 72-h assessment (ITT analysis set)			
Treatment responder, No. (%) [95% CI]	264 (79.5) [74.8 to 83.7]	266 (79.4) [74.7 to 83.6]	0.1 (−6.1 to 6.2)
Cellulitis/erysipelas, No./total (%)	101/135 (74.8)	100/139 (71.9)	
Major cutaneous abscess, No./total (%)	80/100 (80.0)	84/98 (85.7)	
Wound infection, No./total (%)	83/97 (85.6)	82/98 (83.7)	
Treatment nonresponder or indeterminate, No. (%)[a]	68 (20.5)	69 (20.6)	
Treatment nonresponder	27 (8.1)	35 (10.4)	
Indeterminate	41 (12.3)	34 (10.1)	
Missing lesion measurements	22 (6.6)	24 (7.2)	
Missing temperature data	37 (11.1)	32 (9.6)	
Sustained at the EOT assessment (ITT analysis set)			
Clinical success, No. (%) [95% CI]	230 (69.3) [64.0 to 74.2]	241 (71.9) [66.8 to 76.7]	−2.6 (−9.6 to 4.2)
Cellulitis/erysipelas, No./total (%)	85/133 (63.9)	84/135 (62.2)	
Major cutaneous abscess, No./total (%)	72/100 (72.0)	78/97 (80.4)	
Wound infection, No./total (%)	73/99 (73.7)	79/103 (76.7)	
Clinical treatment failure or indeterminate, No. (%)	102 (30.7)	94 (28.1)	
Clinical treatment failure	60 (18.1)	61 (18.2)	
Indeterminate	42 (12.7)	33 (9.9)	
Lost to follow-up	14 (4.2)	14 (4.2)	
Gram-negative infection	4 (1.2)	3 (0.9)	
Withdrew consent	6 (1.8)	2 (0.6)	
Indeterminate at the 48- to 72-h assessment	33 (9.9)	26 (7.8)	
Pregnancy	1 (0.3)	1 (0.3)	

Efficacy - Establish-2 study

tedizolid

Lancet Infect Dis 2014; 14: 696–705

- Randomized, double-blind, double-dummy, multicenter, phase 3 noninferiority trial
- 666 patients (age ≥ 12 yrs.) with ABSSSI (Gram + organism suspected or documented)
- Randomized 1:1 to receive IV treatment of
  - Tedizolid 200 mg once daily x 6 days (n=332)
  - Linezolid 600 mg BID x 10 days (n=334)
- Optional oral step-down allowed after 2 IV doses
- Primary efficacy endpoint
  - Early clinical response at the 48-72 hour assessment
  - 10% noninferiority margin was predefined

Efficacy - Establish-2 study

tedizolid

Lancet Infect Dis 2014; 14: 696–705

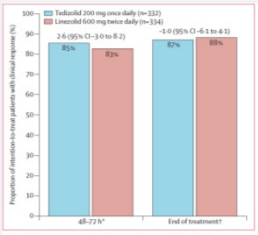


Figure 2: Clinical response rates based on objective assessments incorporating changes in lesion area, at 48–72 h (primary efficacy endpoint) and at end of treatment (secondary efficacy endpoint) in the intention-to-treat population

	Tedizolid phosphate (n=332)	Linezolid (n=334)	Difference (95% CI)
48–72 hours*	304 (92%)	302 (90%)	1·2% (−3·3 to 5·6)
Day 7*	309 (93%)	308 (92%)	0·9% (−3·2 to 4·9)
End of treatment (day 11)†	304 (92%)	301 (90%)	1·4% (−3·0 to 5·9)
Post-therapy assessment (7–14 days after end of treatment)†	292 (88%)	293 (88%)	0·3% (−4·8 to 5·3)
Late follow-up (18–25 days after end of treatment)‡	262/268 (98%)	266/269 (99%)	−1·1% (−3·8 to 1·3)

Data are n (%), unless otherwise indicated. ABSSSI=acute bacterial skin and skin-structure infection. *Clinical success defined as improvement in overall clinical status of ABSSSI compatible with continuation of study drug. †Clinical success defined as resolution or near resolution of disease-specific signs and symptoms, absence or near resolution of baseline systemic signs of infection, and no further antibiotic treatment required for treatment of primary ABSSSI lesion. ‡Clinical success defined as no new signs or symptoms of primary ABSSSI after post-therapy assessment. Only assessed in patients who were clinically evaluable and deemed clinical successes at post-therapy assessment.

Table 3: Investigator-assessed clinical success rates

Price

- How Supplied
  - 200 mg tablets
  - 200 mg lyophilized powder for injection in single-use vials
- AWP
  - PO - $354 each; $2,124 per 6-day regimen
  - IV - $282 each; $1,692 per 6-day regimen
- Comparator
  - Zyvox (linezolid) PO - $169.47 each; $3,389-4,745 per 10-14 days
    IV - $174.33 each; $3,487-4,881 per 10-14 days

tedizolid

Simplicity

tedizolid

- 200 mg IV/PO once daily for 6 days
- PO dose can be given with or without food
- IV dose is diluted in 250 ml NS and administered over 1 hour
  - Do not shake vial during reconstitution due to foaming
  - Use within 24 hours
- No dosing adjustment needed in elderly or renal/hepatic impairment

Vs. linezolid

- 6 day vs. 10-14 day course
- Once daily vs. BID dosing
- Less potential for drug interactions / ADR
- Single indication currently
- Less familiarity

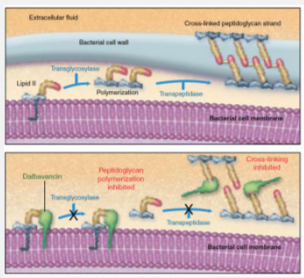
Dalvance® (dalbavancin)

- Category
  - Lipoglycopeptide antibiotic
- Indication
  - treatment of adult patients with ABSSSI caused by:
    - *Staphylococcus aureas* (including MRSA)
    - *Streptococcus pyogenes / agalactiae*
    - *Streptococcus anginosis* group

Mechanism of Action

dalbavancin

- Interferes with cell wall synthesis
- Binds to D-alanyl-D-alanine terminus and prevents cross-linking
- Bactericidal
- Half-life = 2 weeks



AJHP 2008; 65:599-610

dalbavancin

Safety

- Hypersensitivity reactions
  - Both anaphylactic and skin reactions have been reported
  - Cross-sensitivity with other glycopeptides is possible
- Infusion related reactions – "Red-Man Syndrome"
- Hepatic effects – ALT elevation (≥3X ULN)
  - 12 (0.8%) vs. 2 (0.2%) for comparators
- CDAD
- Development of drug-resistant bacteria

dalbavancin

Tolerability

Table 1. Selected Adverse Reactions in Phase 2/3 Trials (Number (%) of Patients)

	Dalbavancin (N = 1778)	Comparator* (N = 1224)
Nausea	98 (5.5)	78 (6.4)
Vomiting	50 (2.8)	37 (3)
Diarrhea	79 (4.4)	72 (5.9)
Headache	83 (4.7)	59 (4.8)
Rash	48 (2.7)	30 (2.4)
Pruritus	38 (2.1)	41 (3.3)

* Comparators included linezolid, cefazolin, cephalexin, and vancomycin.

dalbavancin

Efficacy – DISCOVER trials

N Engl J Med 2014;370:2169-79.

- DISCOVER 1 & DISCOVER 2 – Identical double-blind, double-dummy, multicenter, randomized trials
- 1,312 adult patients with ABSSSI
- Randomized 1:1 to either
  - dalbavancin 1g IV on day 1, followed by 500 mg IV on day 8 (n=288/371)
  - vancomycin 1g (or 15 mg/kg) IV q12h for 10-14 days (n=285/368)
    - Allowed for pharmacist dose adjustment
    - After 3 days, a switch to PO linezolid 600 mg q12h was permitted
- Endpoints (10% noninferiority margin)
  - Primary – early clinical response (48 to 72 hr.)
  - Secondary – clinical status & investigator's assessment of outcomes

Efficacy – DISCOVER trials

dalbavancin

N Engl J Med 2014;370:2169-79.

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Dalbavancin	Vancomycin–Linezolid	Absolute Difference (95% CI)
	number/total number (percent)		*percentage points*
Primary end point			
DISCOVER 1	240/288 (83.3)	233/285 (81.8)	1.5 (−4.6 to 7.9)
DISCOVER 2	285/371 (76.8)	288/368 (78.3)	−1.5 (−7.4 to 4.6)
Both trials	525/659 (79.7)	521/653 (79.8)	−0.1 (−4.5 to 4.2)
Sensitivity analysis			
DISCOVER 1	259/288 (89.9)	259/285 (90.9)	−1.0 (−5.7 to 4.0)
DISCOVER 2	325/371 (87.6)	316/368 (85.9)	1.7 (−3.2 to 6.7)
Both trials	584/659 (88.6)	575/653 (88.1)	0.6 (−2.9 to 4.1)
Secondary end point			
Clinical status	517/570 (90.7)	502/545 (92.1)	−1.5 (−4.8 to 1.9)
Sensitivity analysis of clinical status†	533/570 (93.5)	517/545 (94.9)	−1.4 (−4.2 to 1.4)
Investigator's assessment of outcome	547/570 (96.0)	527/545 (96.7)	−0.7 (−3.0 to 1.5)

* The primary end point was the success rate at 48 to 72 hours after the initiation of therapy (i.e., early clinical response) in the intention-to-treat population. The sensitivity analysis of the primary end point was the success rate, defined as a reduction in the infection area of at least 20% at 48 to 72 hours after the initiation of therapy, in the intention-to-treat population. The secondary end points were evaluated in a pooled analysis and included success rates at the end of therapy in the clinical per-protocol population. For the pooled analysis, the weighted difference in success rates was calculated.
† The degree of fluctuance or localized heat or warmth had to be improved from baseline.

Price

dalbavancin

- How Supplied
  - 500 mg single-use vials containing sterile powder
  - Store at room temp
- AWP - $1,788 each or $5,364 per treatment
- Comparator
  - Vancocin® (vancomycin) - $6-7 per 1g vial ($168-196 per 14-days)
  - Vibativ® (telavancin) - $371.36 per 750 mg vial ($5,199 per 14 days)
  - Orbactiv® (oritavancin) - $1,160 per 400 mg vial ($3,480 per treatment)

http://www.nature.com/nm/journal/v20/n7/full/nm0714-690.html

Simplicity

dalbavancin

- Recommended 2-dose regimen
  - 1000 mg followed one week later by 500 mg
- Renal dose adjustment for CrCl < 30 ml/min, not on HD
  - 750 mg followed one week later by 375 mg
- Administer as IVPB over 30 minutes
- Reconstitute with 25 ml sterile water; do not shake
- Dilute only with D_5W to final concentration 1 to 5 mg/ml
- Saline-based IV solutions may cause precipitation
- Expiration – 48 hours

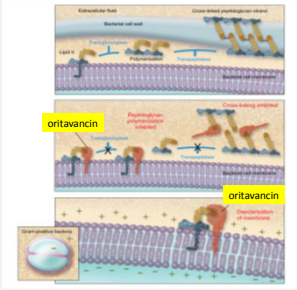
Orbactiv® (oritavancin)

- Category
  - Lipoglycopeptide antibiotic
- Indication
  - treatment of adult patients with ABSSSI caused by:
    - *Staphylococcus aureas* (including MRSA)
    - *Streptococcus pyogenes / agalactiae / dysgalactiae*
    - *Streptococcus anginosis* group
    - *Enterococcus faecalis* (vanc-susceptible isolates only)

Mechanism of Action

oritavancin

- Inhibits cell wall synthesis by:
  - Inhibition of transglycosylation (polymerization) step
  - Inhibition of transpeptidation (crosslinking)
- Disruption of bacterial membrane integrity leading to depolarization
- Bactericidal
- Half-life = 10 days



AJHP 2007; 64:2335-48

Safety

oritavancin

- IV Heparin use contraindicated for 48 hours after administration
  - Falsely elevates aPTT test results for 48 hours
  - Could use Factor Xa assay if therapy necessary
- Increased risk of bleeding when given with warfarin
  - Monitor for s/s of bleeding
  - PT/INR artificially prolonged for 24 hours
  - Use only when benefits outweigh risk of bleeding

oritavancin

Safety

- Hypersensitivity reactions
  - Cross-sensitivity with other glycopeptides possible
- Infusion related reactions - "Red Man's Syndrome"
- Osteomyelitis
  - More cases reported with oritavancin than for vancomycin
  - Monitor patient for signs & symptoms
- CDAD
- Development of drug resistant bacteria

oritavancin

Tolerability

Most Common ADRs (≥3%)

- Headache
- Nausea
- Vomiting
- Limb & subcutaneous abscess
- Diarrhea
- ALT increase (2.8%)
- Tachycardia (2.5%)

Drug Interaction

- Weak inhibitor of CYP2C9 & CYP2C19
- Weak inducer of CYP3A4 & CYP2D6
- May be of concern in drugs with narrow therapeutic index

oritavancin

Efficacy - SOLO 1 trial

N Engl J Med 2014;370:2180-90.

- Randomized, double-blind, international, phase 3 trial
- 954 adult patient diagnosed with ABSSSI
- Randomized 1:1 to receive
  - oritavancin 1200 mg - single IV dose (n=475)
  - vancomycin 1 g (or 15 mg/kg) q12h x 7-10 days (n=479)
- Endpoints (10% noninferiority margin)
  - Primary - cessation of spreading or reduction in lesion size, absence of fever, and no need for a rescue antibiotic at 48 to 72 hours
  - Secondary - clinical cure at 7-14 days, reduction in lesion size of 20% or more at 48-72 hours

Efficacy – SOLO 1 trial

oritavancin

N Engl J Med 2014;370:2180-90.

Subgroup	Oritavancin	Vancomycin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
Modified intention-to-treat population			
Primary efficacy outcome at ECE	391/475 (82.3)	378/479 (78.9)	3.4 (−1.6 to 8.4)
Investigator-assessed clinical cure at PTE	378/475 (79.6)	383/479 (80.0)	−0.4 (−5.5 to 4.7)
Lesion size reduction ≥20% at ECE	413/475 (86.9)	397/479 (82.9)	4.1 (−0.5 to 8.6)
CE population			
Primary efficacy outcome at ECE	344/394 (87.3)	342/397 (86.1)	1.2 (−3.6 to 5.9)
Investigator-assessed clinical cure at PTE	357/394 (90.6)	352/397 (88.7)	1.9 (−2.3 to 6.2)
Lesion size reduction ≥20% at ECE	362/394 (91.9)	370/397 (93.2)	−1.3 (−5.0 to 2.3)
Patients infected with MRSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	84/104 (80.8)	80/100 (80.0)	0.8 (−10.1 to 11.7)
Investigator-assessed clinical cure at PTE	86/104 (82.7)	83/100 (83.0)	−0.3 (−10.7 to 10.0)
Lesion size reduction ≥20% at ECE	94/104 (90.4)	84/100 (84.0)	6.4 (−2.8 to 15.5)
Patients infected with MSSA in intention-to-treat population with microbiologic evaluation			
Primary efficacy outcome at ECE	96/116 (82.8)	92/110 (83.6)	−0.9 (−10.6 to 8.9)
Investigator-assessed clinical cure at PTE	89/116 (76.7)	88/110 (80.0)	−3.3 (−14.0 to 7.4)
Lesion size reduction ≥20% at ECE	98/116 (84.5)	94/110 (85.5)	−1.0 (−10.3 to 8.3)

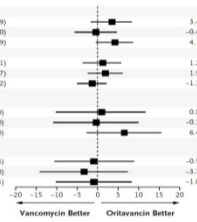
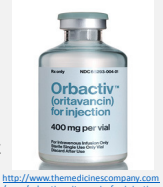


Figure 2. Primary and Secondary Efficacy End Points According to Analysis Population and MRSA Subgroup.
CE denotes clinical evaluation, ECE early clinical evaluation, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-susceptible *S. aureus*, and PTE post-therapy evaluation.

Price

oritavancin

- How Supplied
  - 400 mg single-use vials (lyophilized powder)
  - Stored at room temp
- AWP - $1,160 per vial or $3,480 per treatment
- Comparator (AWP)
  - Vancocin® (vancomycin) - $6-7 per 1g vial ($168-196 per 14-days)
  - Vibativ® (telavancin) - $371.36 per 750 mg vial ($5,199 per 14 days)
  - Dalvance® (dalbavancin) - $1,788 each ($5,364 per treatment)



http://www.themedicinescompany.com/page/orbactiv-oritavancin-for-injection

Simplicity

oritavancin

- Recommended dose – 1,200 mg IVPB as single dose
- Administer over 3 hours
- Reconstitute each vial with 40 ml sterile water
- Gently swirl to avoid foaming
- Dilute in 1L of D_5W (product is incompatible in saline)
- Withdraw 120 ml from liter bag prior to adding drug
- Expiration – 6 hrs room temp / 12 hrs refrigerated

QUESTION #3

When compared to linezolid, which is NOT a potential advantage of tedizolid?

A. Once daily dosing

B. Shorter course of therapy for treatment of skin infections

C. Less potential to cause drug-drug interactions

D. Higher number of FDA-approved indications

QUESTION #3

When compared to linezolid, which is NOT a potential advantage of tedizolid?

A. Once daily dosing

B. Shorter course of therapy for treatment of skin infections

C. Less potential to cause drug-drug interactions

D. Higher number of FDA-approved indications

QUESTION #4

Which new antibiotic is approved to treat acute bacterial skin and skin structure infections (ABSSSI) with a single IV dose?

A. Dalvance® (dalbavancin)

B. Orbactiv® (oritavancin)

C. Sivextro® (tedizolid)

D. Vibativ® (telavancin)

QUESTION #4

Which new antibiotic is approved to treat acute bacterial skin and skin structure infections (ABSSSI) with a single IV dose?

A. Dalvance® (dalbavancin)

B. Orbactiv® (oritavancin)

C. Sivextro® (tedizolid)

D. Vibativ® (telavancin)

Striverdi Respimat® (olodaterol)

- Category
  - Long-acting beta$_2$-adrenergic agonist (LABA)
- Indication
  - long-term, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
  - NOT indicated for acute symptom or asthma treatment

Mechanism of Action

olodaterol

- Activation of beta$_2$-receptors results in stimulation of intracellular adenyl cyclase, which synthesizes cAMP
- cAMP elevation results in relaxation of airway smooth muscles – leading to bronchodilation

olodaterol

Safety

BLACK BOX WARNING - Asthma-Related Death

- LABAs increase risk of asthma-related deaths
- Class effect - data is with salmeterol
- Contraindicated in asthma without use of a long-term control medication
- Do not use in patients with acutely deteriorating COPD
- Paradoxical bronchospasm may occur
- Use with caution in patients with convulsive disorders, thyrotoxicosis, QT-prolongation, or increased sensitivity to sympathomimetics
- Hypersensitivity reactions may occur

olodaterol

Tolerability

Most Common ADRs (≥2%)

- Nasopharyngitis
- Upper respiratory tract infection
- Bronchitis
- Urinary tract infection
- Cough
- Dizziness
- Rash
- Diarrhea
- Back pain
- Arthralgia

Drug Interactions

- Other adrenergic drugs
  - May potentiate effects
- Xanthine derivatives, steroids, diuretics
  - May potentiate hypokalemia
- MAO-I's, TCAs, QT-prolonging drugs
  - May potentiate CV effects
- Beta-blockers
  - May decrease effectiveness

olodaterol

Efficacy

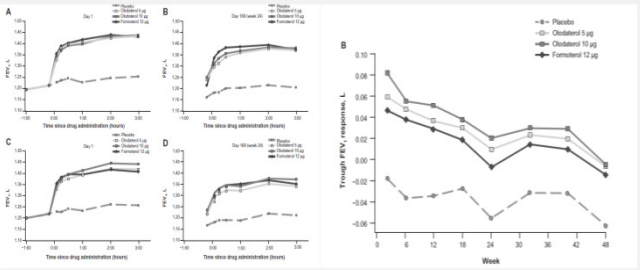
International Journal of COPD 2014:9 697–714

- Two replicate, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group, Phase III studies
- 1,838 patients with COPD; age ≥40
- Randomized to receive
  - Olodaterol 5 mg once daily (n=227 / 232)
  - Olodaterol 10 mg once daily (n=225 / 234)
  - Formoterol 12 mcg BID (n=227 / 233)
  - Placebo (n=225 / 235)
- Primary Outcomes
  - FEV_1 area under the curve from 0-3 hours (AUC_{0-3}) response
  - Trough FEV_1 response after 24 weeks of treatment

Efficacy

International Journal of COPD 2014:9 697–714

olodaterol



FEV_1 AUC_{0-3}

Trough FEV_1 AUC

Price

http://www.empr.com/striverdi-respimat-inhaler-approved-for-copd/article/363863/

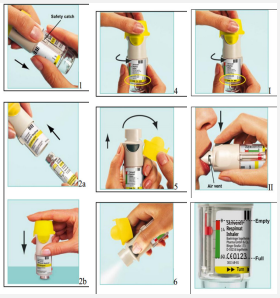
- How Supplied
  - Respimat inhaler and cartridge
  - Each actuation delivers 2.5 mcg of olodaterol
- AWP - $186.84
- Comparators
  - Serevent Diskus® (salmeterol) - $277.20
  - Arcapta Neohaler® (indacaterol) - $220.04
  - Foradil Aerolizer® (formoterol) - $276.34

http://www.medicines.org.uk/emc/medicine/28992

olodaterol

Simplicity

- 2 inhalations once daily at the same time of day
- Do not exceed 2 inhalations/day
- Unit must be primed
- No dose adjustments necessary for elderly or renal/hepatic impairment



https://www.striverdi.com/content/dam/internet/pm/striverdi/com_EN/documents/Striverdi_EU_SPC.pdf

olodaterol

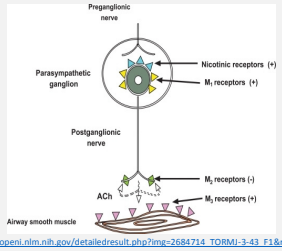
Incruse Ellipta® (umeclidinium)

- Category
  - Inhaled anticholinergic
  - Long-acting muscarinic antagonist (LAMA)
- Indication
  - Long-term, maintenance treatment of airflow obstruction in patients with COPD

Mechanism of Action

umeclidinium

- Long-acting, antimuscarinic agent
- Similar affinity for muscarinic receptors M1 to M5
- Bronchodilation effects are due to inhibition of M3 receptors in smooth muscles of the airway
- Half-life = 11 hours



http://openi.nlm.nih.gov/detailedresult.php?img=2684714_TORMJ-3-43_F1&req=4

Safety

umeclidinium

- Contraindicated in patients with severe hypersensitivity to milk protein
- Do not initiate in acutely deteriorating COPD
- Paradoxical bronchoconstriction
- Narrow-angle glaucoma
- Worsening of urinary retention
  - Use with caution in patients with BPH

umeclidinium

Tolerability

Most Common ADRs (≥2%)

- Nasopharyngitis
- Upper respiratory tract infection
- Cough
- Arthralgia

Drug Interactions

- Other anticholinergic drugs
  - Additive effects

umeclidinium

Efficacy *Eur Respir J* 2014; 43: 72-81

- 12-week, randomized, double-blind, placebo-controlled, parallel-group study
- 206 patients ≥40 years old with COPD
- Randomized 1:1:1 to receive
  - umeclidinium 62.5 mg once daily (n=69)
  - umeclidinium 125 mg once daily (n=69)
  - or placebo once daily (n=68)
- Primary efficacy endpoints
  - Trough FEV_1 on day 85

umeclidinium

Efficacy *Eur Respir J* 2014; 43: 72-81

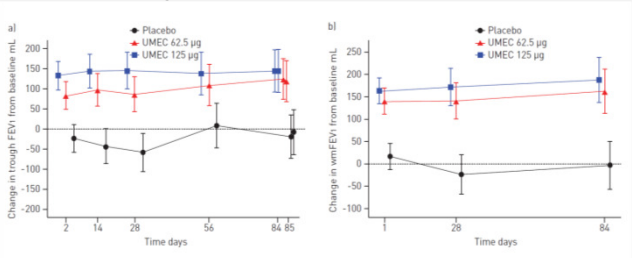


FIGURE 2 Change from baseline in a) trough forced expiratory volume in 1 s (FEV1) and b) 0–6-h weighted mean FEV1 (wmFEV1) (intent-to-treat population). Data are presented as least squares means with 95% confidence intervals. UMEC: umeclidinium bromide.

Price

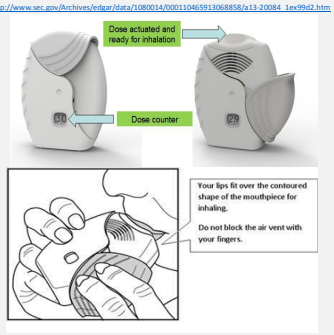
- How Supplied
  - Disposable dry-powder inhaler
  - Double-foil blister strip with 30 blisters
  - Delivers 62.5 mcg of umeclidinium per inhalation
  - Discard 6 weeks after opening or when counter reads "0"
- Not yet marketed – anticipated launch is 4th quarter of 2014
- Expected to have similar price as competitors (AWP)
  - Spiriva HandiHaler (tiotropium) - $351.18
  - Tudorza Pressair (aclidinium) - $307.26

umeclidinium

Simplicity

- 1 inhalation once daily
- No dosage adjustment needed for geriatric patients or for renal/hepatic impairment
- Combined with vilanterol (LABA) in product Anoro Ellipta®
  - Approved in Dec 2013
  - Once daily using same DPI technology

http://www.sec.gov/Archives/edgar/data/1080014/000110465913068858/a13-20084_1ex99d2.htm



umeclidinium

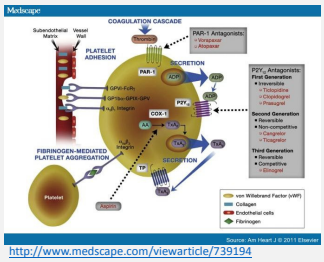
Zontivity® (vorapaxar)

- Category
  - Protease-activated receptor-1 (PAR-1) antagonist
- Indication
  - Reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD)
  - Reduces rate of combined endpoint of CV death, MI, stroke, and urgent coronary revascularization

Mechanism of Action

vorapaxar

- Reversible antagonist of the protease-activated receptor-1 (PAR-1) expressed on platelets
- Long half-life (3-4 days) makes it effectively irreversible
- Inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation



http://www.medscape.com/viewarticle/739194

Safety

vorapaxar

BLACK BOX WARNING - Bleeding Risk

- Do not use in patients with a history of stroke, TIA, or intracranial hemorrhage (ICH) or active bleeding
- Increases risk of bleeding, including ICH and fatal bleeds
- Avoid use with strong CYP3A inhibitors or inducers

Tolerability - TRA 2P-TIMI 50 study

	Vorapaxar	Placebo	Hazard Ratio	P value
Bleeding	13,186	13,166		
GUSTO moderate or severe	438 (4.2)	267 (2.5)	1.66 (1.43–1.93)	<0.001
TIMI				
Clinically significant	1759 (15.8)	1241 (11.1)	1.46 (1.36–1.57)	<0.001
Non–CABG-related major	287 (2.8)	198 (1.8)	1.46 (1.22–1.75)	<0.001
CABG-related major†	11 (7.6)	10 (6.1)	1.13 (0.48–2.66)	0.79
Fatal	29 (0.3)	20 (0.2)	1.46 (0.82–2.58)	0.19
Intracranial	102 (1.0)	53 (0.5)	1.94 (1.39–2.70)	<0.001
Intracerebral	89 (0.8)	41 (0.4)	2.19 (1.51–3.17)	<0.001
Subdural or epidural	12 (0.1)	10 (0.1)	1.20 (0.52–2.79)	0.67
Unknown	1 (<0.1)	2 (<0.1)		

N Engl J Med 2012;366:1404-13.

- Because older patients are generally at a higher risk of bleeding, consider patient age before initiating vorapaxar

vorapaxar

Efficacy - TRA 2P-TIMI 50 trial

vorapaxar

N Engl J Med 2012;366:20-33.

- Multinational, double-blind, placebo-controlled trial
- 26,449 patients with history of MI, ischemic stroke, or peripheral arterial disease – 94% on ASA, majority of MI dx on thienopyridine
- Randomly assigned in a 1:1 ratio to receive vorapaxar 2.5 mg once daily or matched placebo
- Primary efficacy end-point
  - Composite of CV death, MI, or stroke
- Secondary end-point
  - Composite of CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization
- Stopped early after 2 years in patients with h/o of stroke

Efficacy - TRA 2P-TIMI 50 trial

vorapaxar

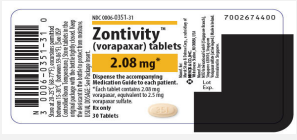
N Engl J Med 2012;366:20-33.

Table 2. Efficacy and Bleeding End Points at 3 Years.*

End Point	Vorapaxar	Placebo	Hazard Ratio (95% CI)	P Value
	number (percent)			
Efficacy	13,225	13,224		
Cardiovascular death, myocardial infarction, or stroke	1028 (9.3)	1176 (10.5)	0.87 (0.80–0.94)	<0.001
Cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization	1259 (11.2)	1417 (12.4)	0.88 (0.82–0.95)	0.001
Cardiovascular death or myocardial infarction	789 (7.3)	913 (8.2)	0.86 (0.78–0.94)	0.002
Cardiovascular death	285 (2.7)	319 (3.0)	0.89 (0.76–1.04)	0.15
Myocardial infarction	564 (5.2)	673 (6.1)	0.83 (0.74–0.93)	0.001
Stroke				
Any stroke	315 (2.8)	324 (2.8)	0.97 (0.83–1.14)	0.73
Ischemic stroke	250 (2.2)	294 (2.6)	0.85 (0.72–1.01)	0.06
Urgent coronary revascularization	279 (2.5)	316 (2.6)	0.88 (0.75–1.03)	0.11
Death from any cause	540 (5.0)	565 (5.3)	0.95 (0.85–1.07)	0.41
Net clinical outcome	13,186	13,166		
Cardiovascular death, myocardial infarction, stroke, or GUSTO moderate or severe bleeding	1315 (11.7)	1358 (12.1)	0.97 (0.90–1.04)	0.40
Cardiovascular death, myocardial infarction, stroke, urgent coronary revascularization, or GUSTO moderate or severe bleeding	1526 (13.4)	1593 (14.0)	0.96 (0.89–1.02)	0.20
Death from any cause, myocardial infarction, stroke, or GUSTO severe bleeding	1322 (11.9)	1436 (12.8)	0.92 (0.85–0.99)	0.02

Price

- How Supplied
  - 2.08 mg tablets
  - Store in original package



- AWP - $10.69 each - $320 per month

vorapaxar

Simplicity

vorapaxar

- Dosing – 1 tablet (2.08 mg) PO once daily
  - with or without food
- Take with aspirin and/or clopidogrel
- No dose adjustment for renal or hepatic function
- No antidote to reverse antiplatelet effect

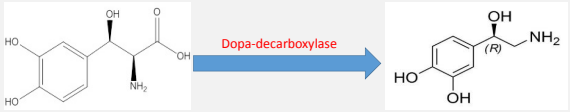
Northera® (droxidopa)

- Category
  - Vasopressor
  - Synthetic amino acid precursor of norepinephrine
- Indication
  - Treatment of **symptomatic neurogenic orthostatic hypotension (NOH)**
    - Primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure)
    - Dopamine beta-hydroxylase deficiency
    - Non-diabetic autonomic neuropathy
  - Effectiveness beyond 2 weeks of treatment has not been demonstrated.

Mechanism of Action

droxidopa

- Metabolized to norepinephrine by dopa-decarboxylase
- Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction



Droxidopa
L-dihydroxyphenylserine (L-DOPS)

norepinephrine

droxidopa

Safety

BLACK BOX WARNING - SUPINE HYPERTENSION

- Monitor supine blood pressure prior to and during treatment
- Elevating head of the bed lessens risk
- Reduce dose or discontinue if supine hypertension continues

- Hyperpyrexia and Confusion
  - Symptom complex resembling neurologic malignant syndrome (NMS)
  - Post-marketing reports in Japan
  - Observe closely during dosage changes or if concomitant levodopa dose is reduced or discontinued

droxidopa

Safety

- Ischemic heart disease, Arrhythmias, and CHF
  - May be exacerbated by droxidopa
  - Carefully consider potential risks prior to initiating therapy

- Allergic Reactions
  - 300 mg capsule contains FD&C Yellow #5 (tartrazine)
  - Causes allergic-type reactions in some patients (bronchial asthma)
  - Aspirin-hypersensitivity frequently seen in same patients

droxidopa

Tolerability

Most common ADRs (>5%)

- Headache
- Dizziness
- Nausea
- Hypertension
- Fatigue

Drug Interactions

- Drugs that increase blood pressure
  - Norepinephrine, ephedrine, midodrine, and triptans
- Parkinson's Medications
  - Dopa-decarboxylase inhibitors may require dose adjustments

Efficacy

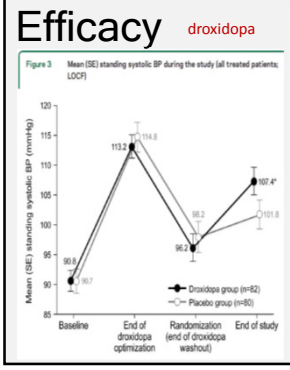
droxidopa

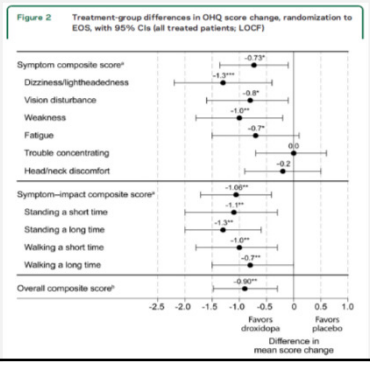
Neurology 2014;83:328-335

- Randomized, placebo-controlled, parallel-group trial
- 162 patients with Parkinson disease, multiple system atrophy, pure autonomic failure, or non-diabetic autonomic neuropathy
- Open-label droxidopa dose optimization (100-600 mg TID), followed, in responders, by 7-day washout and then a 7-day double-blind trial of droxidopa vs placebo
- Primary efficacy endpoint
  - change in overall composite score on the orthostatic hypotension questionnaire (OHQ) from randomization to end of study

Efficacy

droxidopa





Price

droxidopa

- How Supplied - 100, 200, and 300 mg capsules
- Specialty pharmacy drug

http://www.businesswire.com/news/home/20140218006891/en/Chelsea-Therapeutics-Announces-FDA-Accelerated-Approval-NORTHERA%E2%84%A2#.VAm7pfIdXUI

- AWP
  - 100 mg - $18.79 each - $1,690.80 per month
  - 200 mg - $37.57 each - $3,381.60 per month
  - 300 mg - $56.36 each - $5,072.40 per month
  - 600 mg (max dose) - $10,144.80 per month
- Comparators
  - midodrine (10 mg TID) - $4.84 each - $435.60 per month
  - fludrocortisone - (0.1-0.2 mg daily) - $0.80 each - $24-48 per month

Simplicity

droxidopa

- Starting dose – 100 mg TID during the day
  - Upon arising in AM, midday, late afternoon
- Titrate up by 100 mg/dose every 24-48 hours
- Maximum dose - 600 mg TID
- Take consistently with or without food
- Give last dose at least 3 hours prior to bedtime
- Take capsules whole
- Must monitor blood pressure
- No dose available for GFR < 30 ml/min

QUESTION #5

Which is CORRECT regarding vorapaxar?

A. It should not be used with other antiplatelet agents.

B. Vitamin K can be given as an antidote if serious bleeding develops.

C. It should not be used in patients with a history of stroke.

D. It is dosed twice daily.

QUESTION #5

Which is CORRECT regarding vorapaxar?

A. It should not be used with other antiplatelet agents.

B. Vitamin K can be given as an antidote if serious bleeding develops.

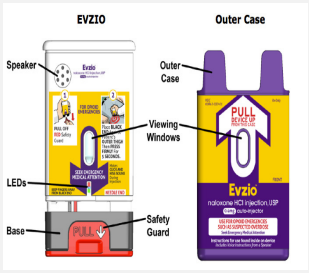
C. It should not be used in patients with a history of stroke.

D. It is dosed twice daily.

Other New Dosage Forms

Evzio®

- New auto-injector formulation for emergency treatment of opioid overdose.
- Visual and voice instructions for guidance
- Inject into thigh
- Will go through clothing
- Seek emergency medical care immediately after use
- AWP - $862.50 for 2



http://www.forbes.com/sites/davidkroll/2014/04/03/fda-rapidly-approves-naloxone-auto-injector-for-heroin-and-prescription-opioid-overdose/2/

Hemangeol®

- Propranolol HCl 4.28 mg/ml oral solution
- Indication - treatment of proliferating infantile hemangioma (≥ 5 weeks old)
- 0.15-0.4 ml/kg (0.6-1.7 mg/kg) BID
- Alcohol-free, paraben-free, sugar-free
- Propranolol 20 mg/5 ml oral solution also available - contains alcohol (0.6%) and paraben
- AWP cost comparison
  - Hemangeol - $450 per 120-ml bottle
  - Propranolol 20/5 - $12.83 for 120-ml ($53.47/500ml)

http://www.hemangeol.com/hcp/

Invokamet®

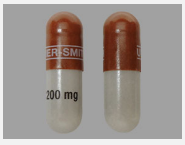
- New combination of canagliflozin + metformin for Type 2 DM
- Taken twice daily with meals
- Same warnings/precautions for each drug applies
- Available strengths
  - 50/500 mg
  - 50/1000 mg
  - 150/500 mg
  - 150/1000 mg
- AWP - $374 per month supply

Purixan®

- First FDA-approved mercaptopurine oral suspension
- Indication – treatment of patients with acute lymphoblastic leukemia (ALL)
- 20 mg/ml – 100 ml bottle
- Previously only available as 50 mg tablets
  - Extemporaneously compounded into suspension in the past
- AWP
  - Purixan - $1,260 per bottle
  - Oral tablets (40) - $163.60

Qudexy XR®

- New extended-release topiramate capsules for seizure indications
- Available strengths
  - 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg
- Taken once daily; dose titrated to seizure control
- Capsules may be opened and contents sprinkled on soft food
- AWP ranges from $5.63 to $19.97 each



http://www.drugs.com/imprints/upsher-smith-200-mg-21940.html

Targiniq ER®

- Combination of oxycodone-naloxone for severe pain
- Abuse-deterrent dosage form designed to interfere with IV or nasal inhalation abuse of these products.
- Naloxone is released and better absorbed if the dosage from is crushed
- Dosed every 12 hours
- Available as 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg tabs
- Swallow whole
- Not yet available – launch date pending

Xartemis XR®

- New extended-release combination product containing oxycodone/acetaminophen for acute, severe pain.
- 2 tablets every 12 hours with or without food
- Swallow whole
- Available as 7.5/325 mg extended-release tablets
- AWP = $2.76 each - $11.04 per day

http://www.mallinckrodt.com/assets/0/95/177/186/2147484013/187/59179b4f-53a9-4bb1-ab8a-2abdfd20e445.jpg?n=9486

New testosterone products

Name	Dosage form	Dosing	AWP
Aveed®	Testosterone undecanoate 250 mg/ml in oil for IM injection	750 mg; repeat in 4 weeks, then every 10 weeks	$990 per 3-ml vial
Natesto®	Intranasal gel in metered dose pump (5.5 mg per actuation)	11 mg (2 pump actuations), one per nostril TID	Not yet marketed
Vogelxo®	1% testosterone topical gel in metered dose pump	50 mg (4 pump actuations) applied to shoulder or upper arm	$233.66 per 75g

New omega-3 products

Epanova®	Omtryg®
• Omega-3-carboxylic acids	• Omega-3-acid ethyl esters A
• 1 gram soft-gelatin capsules	• 1.2 gram soft-gelatin capsules
• Dose – 2-4 caps once daily	• Dose – 4 caps/day in 1-2 doses
• Indicated as an adjunct to diet to reduce triglycerides in adults with severe hypertriglyceridemia (≥500 mg/dl)	• Indicated as an adjunct to diet to reduce triglycerides in adults with severe hypertriglyceridemia (≥500 mg/dl)
• 2014 - 4th quarter launch	• Launch date not yet known

QUESTION #6

The new propranolol oral solution, Hemangeol®, is indicated to treat

A. Infantile hemangioma

B. Hypertension

C. Migraine headache

D. Pheochromocytoma

QUESTION #6

The new propranolol oral solution, Hemangeol®, is indicated to treat

A. Infantile hemangioma

B. Hypertension

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Questions?

Arkansas Drug Information Center
Monday-Friday 8:30 AM to 5 PM

Local: 686-5072
Statewide Tollfree: (888) 228-1233