New Medications & FDA Updates 2017

Suzannah Kokotajlo, PharmD
Morristown Medical Center

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Atlantic Health System

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Disclosures

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.

Pharmacist Objectives

- List the medications that were brought to the market in 2017
- Describe the indications and mechanisms of action of the new medications
- Review adverse effects and patient safety information for these new medications
- Relate new medications approved in 2017 with those approved previously with similar indications
- Discuss important patient counseling and monitoring parameters for newly approved medications
- Identify drug safety warnings that were published by the FDA in 2017

Technician Objectives

- List the medications that were brought to the market in 2017
- Review appropriate storage instructions for the newly approved medications
- Discuss unique preparation instructions for these new medications
- Identify drug safety warnings that were published by the FDA in 2017

New Medications of 2017

- Aliqopa™ (copanlisib)
- Alunbrig® (brigatinib)
- Austedo™ (deutetrabenazine)
- Bavencio® (avelumab)
- **Baxdela™ (delafloxacin)**
- Benznidazole
- Besponsa™ (inotuzumab ozogamicin)
- Bevyxxa® (betrixaban)
- **Brineura™ (cerliponase alfa)**
- Calquence® (acalabrutinib)
- Dupixent® (dupilumab)
- **Emflaza® (deflazacort)**
- Fasenra™ (benralizumab)
- **Giapreza™ (angiotensin II)**
- Hemlibra® (emicizumab)
- Idhifa® (enasidenib)
- Imfinzi® (durvalumab)
- Ingrezza® (valbenazine)
- Kevzara® (sarilumab)
- Kisqali® (ribociclib)
- Macrilen™ (macimorelin acetate)
- Mavyret™ (glecaprevir and pibrentasivir)
- Mepsevii™ (vestronidase alfa)

Source: Novel New Drugs 2017 Summary. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm. Accessed March 19, 2018.

New Medications of 2017

- Nerlynx® (neratinib maleate)
- Ocrevus™ (ocrelizumab)
- **Ozempic® (semaglutide)**
- Parsabiv™ (etelcalcetide)
- Prevymis™ (letermovir)
- **Radicava® (edaravone)**
- Rhopressa® (netarsudil)
- Rydapt® (midostaurin)
- Siliq™ (brodalumab)
- Solosec™ (secnidazole)
- **Steglatro™ (ertugliflozin)**
- Symproic® (naldemedine)
- Tremfya® (guselkumab)
- Trulance® (plecanatide)
- Tymlos™ (abaloparatide)
- **Vabomere™ (meropenem and vaborbactam)**
- Verzenio™ (abemaciclib)
- Vosevi® (sofosbuvir, velpatasivir, and voxilaprevir)
- Vyzulta™ (latanoprostene bunod ophthalmic solution)
- Xadago® (safinamide)
- Xepi™ (ozenoxacin)
- Xermelo™ (telotristat ethyl)
- Zejula® (niraparib)

Source: Novel New Drugs 2017 Summary. Available at: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm. Accessed March 19, 2018.

Baxdela™ (delafloxacin)

- **Approval date**
  - June 2017
- **FDA approved indications**
  - Treatment of acute bacterial skin and skin structure infections caused by designated susceptible bacteria in adults
- **Mechanism of action**
  - Inhibits bacterial topoisomerase IV and DNA gyrase enzymes
- **Dosing**
  - Intravenous: 300 mg IV Q12 hours
  - Oral: 450 mg PO Q12 hours
  - Renal impairment
    - eGFR 15 to 29 mL/min: IV: 200 mg Q12H; PO: no adjustment needed
    - eGFR < 15 mL/min: IV and PO not recommended
- **Adverse reactions**
  - Tendinitis and tendon rupture
  - Peripheral neuropathy
  - Central nervous system effects
  - Hypersensitivity reactions
  - *Clostridium difficile*-associated diarrhea

Source: Baxdela™ (delafloxacin). Prescribing Information. Lincolnshire, IL. 2017.

Baxdela™ (delafloxacin)

- **Interactions**
  - Antacids containing aluminum or magnesium, sucralfate, iron, multivitamins that contain iron or zinc
- **Monitoring**
  - White blood cell count
  - Signs of infection
  - Serum creatinine
- **Dosage forms available**
  - Intravenous: 300 mg vial
  - Oral: 450 mg tablet
- **Counseling points**
  - Oral tablets must be administered 2 hours before or 6 hours after antacids containing magnesium or aluminum, sucralfate, iron, and multivitamins containing zinc or iron
  - Oral tablets can be taken with or without food
  - If miss a dose, take as soon as possible anytime up to 8 hours prior to the next dose

Source: Baxdela™ (delafloxacin). Prescribing Information. Lincolnshire, IL. 2017.

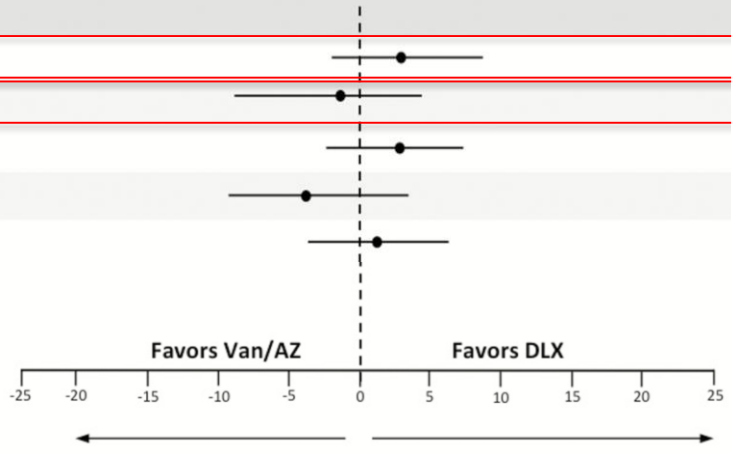
PROCEED Study

- Phase III, multicenter, multinational, stratified, randomized, double-blind trial
  - Delafloxacin
    - eGFR > 29 mL/min
      - 300 mg IV Q12H x 6 doses, then mandatory switch to oral
      - 450 mg orally Q12H for all doses
    - eGFR 15 to 29 mL/min
      - 200 mg IV Q12H for all doses
  - Vancomycin plus Aztreonam
    - eGFR > 29 mL/min
      - Vancomycin 15 mg/kg IV Q12H plus Aztreonam 2 g IV Q12H
    - eGFR 15 to 29 mL/min
      - Vancomycin based on renal dose adjustment plan plus Aztreonam 1 g IV Q12H
- Primary efficacy endpoint
  - US Food and Drug Administration (FDA)
    - Objective response assessment 48 to 72 hours after initiation based on ≥ 20% decrease in lesion size in absence of clinical failure
  - European Medicines Agency (EMA)
    - Investigator assessment of clinical response at the follow-up visit classified as cure, improved, failure or indeterminate
- Safety assessment
  - Physical examination
  - Vital signs
  - 12-lead electrocardiogram
  - Clinical laboratory tests
  - Adverse events

Source: O'Riordan W, McManus A, Teras J, et al. *Clin Infect Dis* 2018;00:1-10.

Results – Efficacy

Subgroup	Delafloxacin	Vancomycin + Aztreonam	Percentage Difference (95% CI)
	events/total (%)		
Intent-to-treat Population Analysis Set (ITT)			
Objective Response at 48 – 72 Hrs.*	354/423 (83.7)	344/427 (80.6)	3.1 (–2.0, 8.3)
Investigator Assessed Cure at FU**	244/423 (57.7)	255/427 (59.7)	– 2.0 (–8.6, 4.6)
Investigator Assessed Success at FU**	369/423 (87.2)	362/427 (84.4)	2.5 (–2.2, 7.2)
Investigator Assessed Cure at LFU	287/423 (67.8)	303/427 (71.0)	–3.1 (–9.3, 3.1)
Investigator Assessed Success at LFU	353/423 (83.5)	351/427 (82.2)	1.3 (–3.8, 6.3)



Source: O'Riordan W, McManus A, Teras J, et al. *Clin Infect Dis* 2018;00:1-10.

Results – Safety

Adverse Event	Delafloxacin (n = 417)	Vancomycin + Aztreonam (n = 425)
Any TEAE affecting ≥ 2% of patients	182 (43.6)	167 (39.3)
Nausea	32 (7.7)	19 (4.5)
Diarrhea	32 (7.7)	14 (3.3)
Infection	16 (3.8)	15 (3.5)
Headache	14 (3.4)	16 (3.8)
Infusion site extravasation	13 (3.1)	10 (2.4)
Pyrexia	11 (2.6)	9 (2.1)
Vomiting	10 (2.4)	8 (1.9)
Increase in creatinine phosphokinase	5 (1.2)	10 (2.4)
TEAE related to study drug	87 (20.9)	89 (20.9)
Any related TEAE resulting in premature study drug discontinuation	5 (1.2)	10 (2.4)
Deaths	0 (0.0)	2 (0.5)

TEAE – treatment-emergent adverse event; Data are presented as no. (%)

Source: O'Riordan W, McManus A, Teras J, et al. *Clin Infect Dis* 2018;00:1-10.

Brineura™ (cerliponase alfa)

- **Approval date**
  - April 2017
- **FDA approved indications**
  - Slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)
- **Mechanism of action**
  - Proenzyme that is taken up by target cells in the CNS and translocated to the lysosomes; activated in the lysosome and then cleaves the polypeptides
- **Dosing**
  - Intraventricular: 300 mg via intraventricular infusion every other week
- **Adverse reactions**
  - Intraventricular access device-related complications
  - Cardiovascular adverse reactions
  - Hypersensitivity

Source: Brineura™ (cerliponase alfa). Prescribing Information. Novato, CA. 2017.

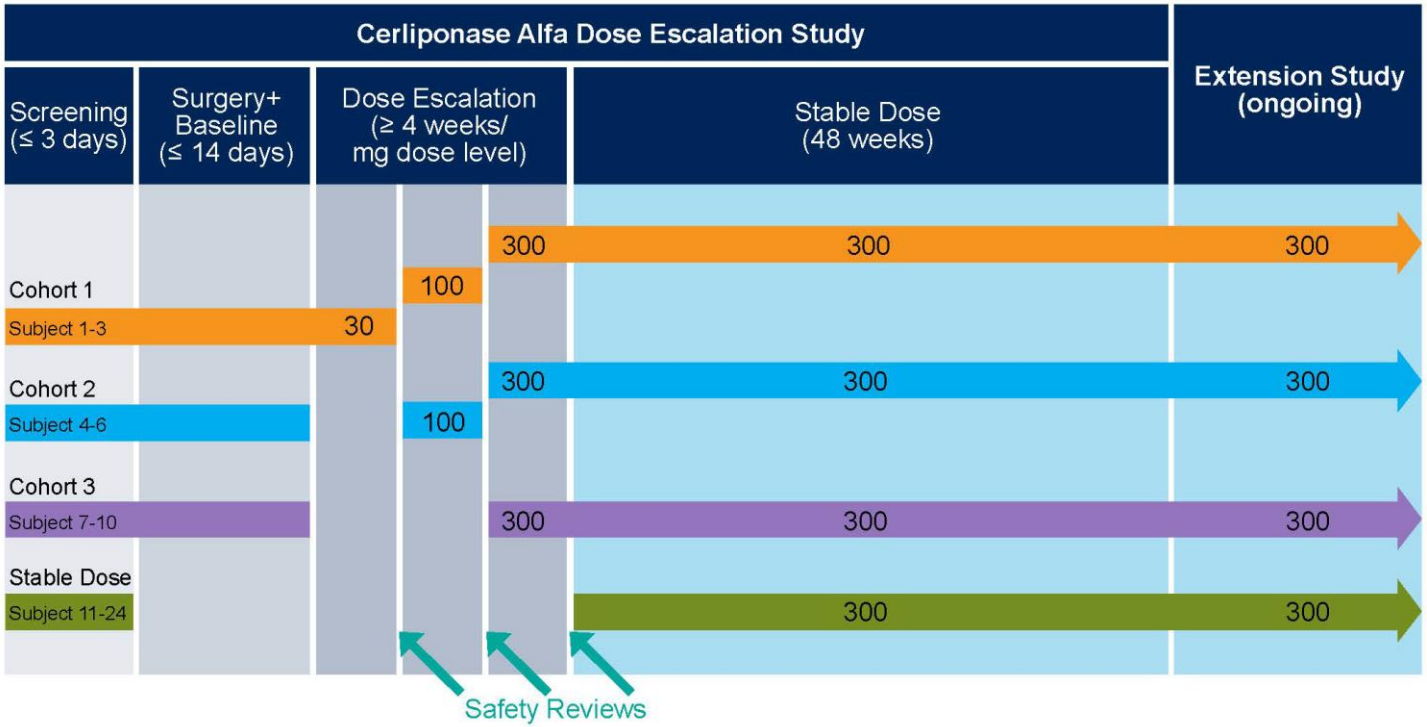
Brineura™ (cerliponase alfa)

- **Interactions**
  - None known
- **Monitoring**
  - CSF studies
  - Other signs of intraventricular device infection
  - Vital signs
  - EKG
- **Dosage forms available**
  - Each kit contains
    - 2 x 150 mg/5 mL vials of Brineura
    - 1 x 5 mL vial of intraventricular electrolytes
- **Counseling points**
  - Risk of intraventricular device infection – notify provider if signs/symptoms of infection

Source: Brineura™ (cerliponase alfa). Prescribing Information. Novato, CA. 2017.

Open-Label Study

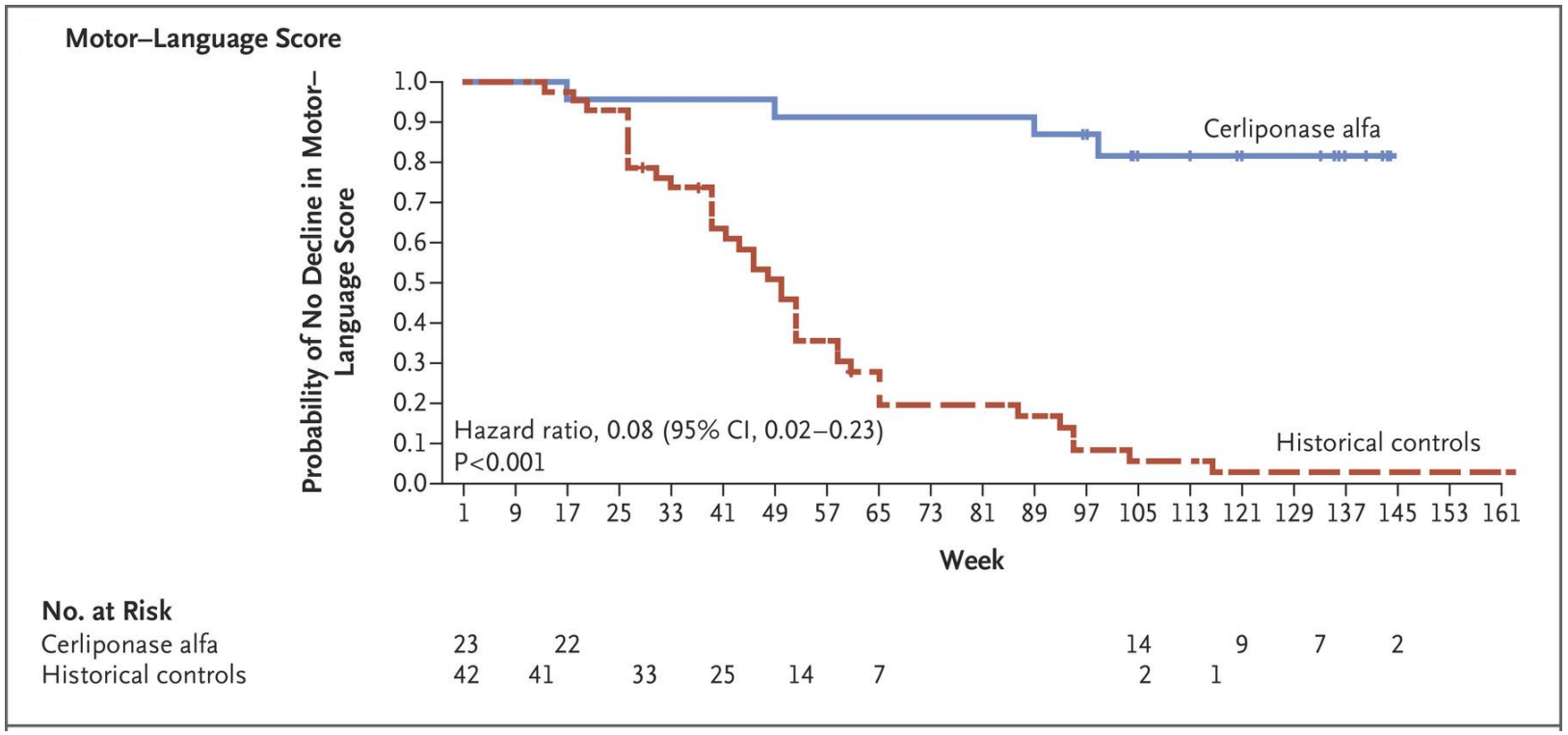
- Multicenter, open-label study



- Primary efficacy outcome
  - Time until the first unreversed 2-point decline in the score on the CLN2 Clinical Rating Scale measuring motor and language skills or until the attainment of a combined motor-language score of 0 as compared with the time in the historical control group
- Safety outcome
  - Adverse events were evaluated at each follow-up appointment

Source: Schulz A, Ajayi T, Specchio N, et al. *N Engl J Med* 2018;378:1898-907.

Results – Efficacy



Source: Schulz A, Ajayi T, Specchio N, et al. *N Engl J Med* 2018;378:1898-907.

Results – Safety

Adverse Event	Patients (N = 24) no. (%)
Common adverse events	
Convulsions	23 (96)
Pyrexia	17 (71)
Vomiting	15 (63)
Hypersensitivity events	15 (63)
Upper respiratory tract infection	13 (54)
Nasopharyngitis	10 (42)
Rhinitis	10 (42)
Serious adverse events	
Any	20 (83)
Hypersensitivity	7 (29)
Upper respiratory tract infection	5 (21)
Epilepsy	4 (17)
Pharyngitis	4 (17)
Gastroenteritis	3 (13)
Pyrexia	2 (8)
Device-related infection	2 (8)

Source: Schulz A, Ajayi T, Specchio N, et al. *N Engl J Med* 2018;378:1898-907.

Emflaza® (deflazacort)

- **Approval date**
  - February 2017
- **FDA approved indications**
  - Treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older
- **Mechanism of action**
  - Corticosteroid prodrug whose active metabolite acts through the glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects
- **Dosing**
  - Oral: 0.9 mg/kg PO once daily
- **Adverse reactions**
  - Immunosuppression / increased risk of infection
  - Alterations in cardiovascular / renal function
  - Behavioral and mood disturbances
  - Effects on bones
  - Serious skin rashes
  - Effects on growth and development
  - Myopathy
  - Thromboembolic events
  - Anaphylaxis

Source: Emflaza® (deflazacort). Prescribing Information. South Plainfield, NJ. 2017.

Emflaza® (deflazacort)

- **Interactions**
  - CYP3A4 inhibitors / inducers
  - Neuromuscular blockers
- **Monitoring**
  - Blood pressure
  - Glucose
  - Electrolytes
  - Growth
  - Signs and symptoms of infection
- **Dosage forms available**
  - Tablets: 6 mg, 18 mg, 30 mg, 36 mg
  - Oral suspension: 22.75 mg/mL
    - 13 mL and 20 mL bottles
- **Counseling points**
  - Take with or without food
  - Do not stop taking medication abruptly
  - Make healthcare professionals aware that medication is being taken

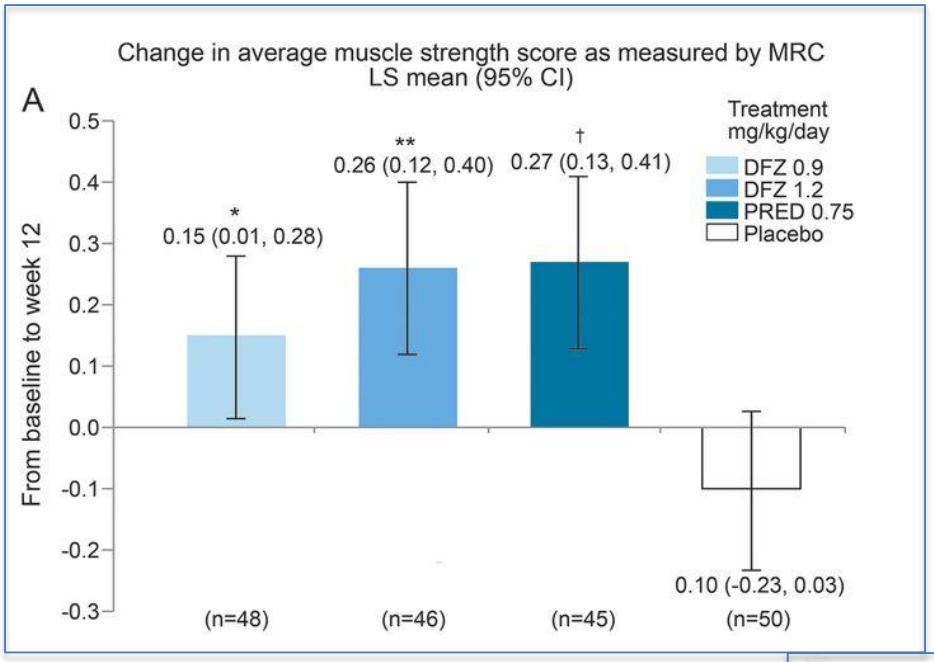
Source: Emflaza® (deflazacort). Prescribing Information. South Plainfield, NJ. 2017.

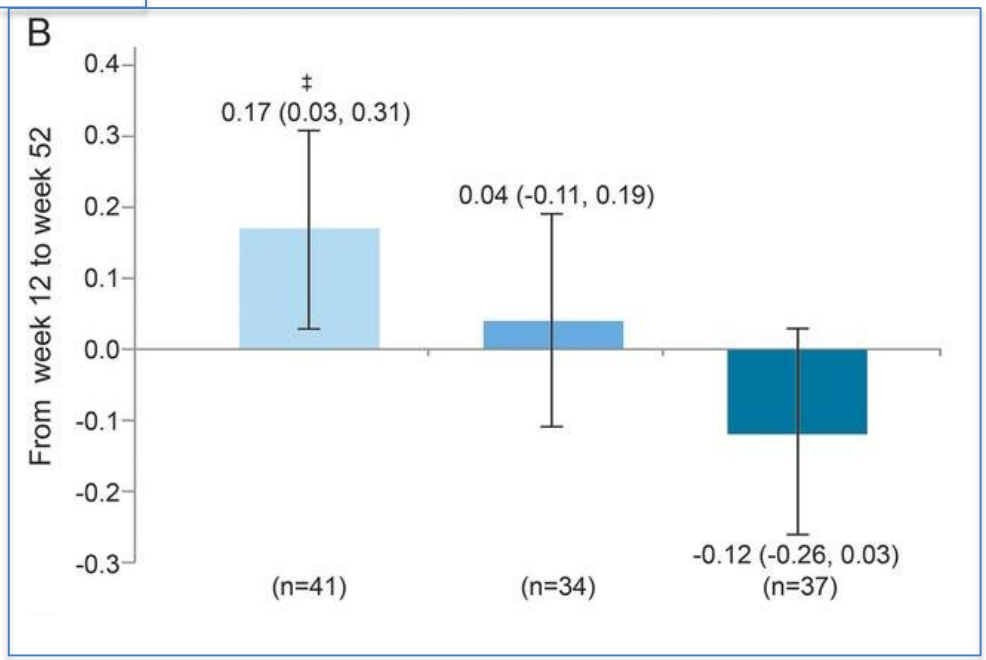
Phase 3 Study

- Multicenter, phase 3, randomized, double-blind, placebo-controlled trial
  - Phase 1: randomly assigned to 4 groups for 12 weeks of treatment
    - Deflazacort 0.9 mg/kg/day
    - Deflazacort 1.2 mg/kg/day
    - Prednisone 0.75 mg/kg/day
    - Placebo
  - Phase 2
    - Placebo treated patients randomly assigned to one of 3 treatment groups and followed for 52 weeks
    - Treatment groups continued for additional 40 weeks
- Primary efficacy assessment
  - Change from baseline to week 12 in average muscle strength as assessed by the modified Medical Research Council (MRC) scale
- Secondary efficacy assessment
  - Change in average muscle strength from week 12 to week 52 and pulmonary function testing
- Safety assessments
  - Incidence of adverse events
  - Changes in clinical laboratory findings or physical examinations
  - Vital signs
  - Change in statural growth percentiles

Source: Griggs RC, Miller JP, Greenberg CR, et al. *Neurology* 2016;87:2123-2131.

Results – Efficacy





Source: Griggs RC, Miller JP, Greenberg CR, et al. *Neurology* 2016;87:2123-2131.

Results – Safety

Adverse event	Deflazacort 0.9 mg/kg/day no. (%)	Deflazacort 1.2 mg/kg/day no. (%)	Prednisone 0.75 mg/kg/day no. (%)	Placebo no. (%)
Participants with ≥ 1 TEAE	58 (85.3)	56 (86.2)	58 (92.1)	38 (76)
Cushingoid	41 (60.3)	45 (69.2)	49 (77.8)	6 (12)
Erythema	19 (27.9)	32 (49.2)	33 (52.4)	3 (6)
Hirsutism	24 (35.3)	24 (36.9)	28 (44.4)	1 (2)
Weight increased	19 (27.9)	21 (32.3)	22 (34.9	3 (6)
Central obesity	17 (25)	16 (24.6)	27 (42.9)	2 (4)

Source: Griggs RC, Miller JP, Greenberg CR, et al. *Neurology* 2016;87:2123-2131.

Giapreza™ (angiotensin II)

- **Approval date**
  - December 2017
- **FDA approved indications**
  - Increase blood pressure in adults with septic or other distributive shock
- **Mechanism of action**
  - Raises blood pressure by vasoconstriction and increased aldosterone release
- **Dosing**
  - Intravenous
    - Initial starting dose: 20 nanograms/kg/min IV
    - Maximum dose: 80 nanograms/kg/min IV
    - Minimum dose: 1.25 nanograms/kg/min IV
- **Adverse reactions**
  - Thrombosis

Source: Giapreza™ (angiotensin II). Prescribing Information. San Diego, CA. 2017.

Giapreza™ (angiotensin II)

- **Interactions**
  - Angiotensin converting enzyme inhibitors may increase the response to angiotensin II
  - Angiotensin II blockers may decrease the response to angiotensin II
- **Monitoring**
  - Blood pressure
- **Dosage forms available**
  - 2.5 mg/mL
  - 1 mL and 2 mL vials
- **Counseling points**
  - Risk of thromboembolic events

Source: Giapreza™ (angiotensin II). Prescribing Information. San Diego, CA. 2017.

ATHOS-3 Study

- International, randomized, double-blind, placebo-controlled
  - Synthetic human angiotensin II or placebo
  - Angiotensin II started at 20 ng/kg/min
    - First 3 hours: study infusion adjusted to achieve mean arterial pressure of 75 mm Hg
      - Max rate of 200 ng/kg/min
    - 3 hours 15 minutes to 48 hours: all infusions titrated to maintain target mean arterial pressure between 65 and 75 mm Hg
      - Dose range of 1.25 to 40 ng/kg/min
    - 48 hours: study infusion discontinued
- Primary efficacy endpoint
  - Response with respect to mean arterial pressure at hour 3
- Safety assessment
  - Serious adverse events
  - Adverse event-related drug discontinuation
  - All adverse events
  - All-cause mortality at 7 days and 28 days

Source: Khanna A, English SW, Wang XS, et al. *N Engl J Med* 2017;377:419-30.

Results – Efficacy

Table 2. Primary and Secondary End Points.*

End Point	Angiotensin II (N=163)	Placebo (N=158)	Odds or Hazard Ratio (95% CI)	P Value
Primary efficacy end point: MAP response at hour 3 — no. (%)†	114 (69.9)	37 (23.4)	Odds ratio, 7.95 (4.76–13.3)	<0.001
Secondary efficacy end points				
Mean change in cardiovascular SOFA score at hour 48‡	−1.75±1.77	−1.28±1.65		0.01
Mean change in total SOFA score at hour 48§	1.05±5.50	1.04±5.34		0.49
Additional end points				
Mean change in norepinephrine-equivalent dose from baseline to hour 3¶	−0.03±0.10	0.03±0.23		<0.001
All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12

* Plus–minus values are means ±SD.
† Response with respect to mean arterial pressure (MAP) at hour 3 after the start of infusion was defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors.
‡ Scores on the cardiovascular Sequential Organ Failure Assessment (SOFA) range from 0 to 4, with higher scores indicating more severe dysfunction.
§ The total SOFA score ranges from 0 to 20, with higher scores indicating more severe dysfunction.
¶ Data were missing for three patients in the angiotensin II group and for one patient in the placebo group.

Source: Khanna A, English SW, Wang XS, et al. *N Engl J Med* 2017;377:419-30.

Results – Safety

Event	Angiotensin II (N = 163) no. (%)	Placebo (N = 158) no. (%)
Adverse event of any grade	147 (87.1)	145 (91.8)
Adverse event leading to discontinuation	23 (14.1)	34 (21.5)
Serious adverse events		
Any	99 (60.7)	106 (67.1)
Infection or infestation	30 (18.4)	21 (13.3)
Cardiac disorder	27 (16.6)	32 (20.3)
Respiratory, thoracic, or mediastinal disorder	17 (10.4)	25 (15.8)
Vascular disorder	17 (10.4)	15 (9.5)
Deep-vein thrombosis	3 (1.8)	0
Intestinal ischemia	1 (0.6)	3 (1.9)

Source: Khanna A, English SW, Wang XS, et al. *N Engl J Med* 2017;377:419-30.

Ozempic® (semaglutide)

- **Approval date**
  - December 2017
- **FDA approved indications**
  - As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **Mechanism of action**
  - Glucagon-like peptide 1 (GLP-1) receptor agonist
- **Dosing**
  - Subcutaneous
    - Initial dose: 0.25 mg subcutaneously once weekly for 4 weeks
    - Maintenance dose: 0.5 to 1 mg subcutaneously once weekly
- **Adverse reactions**
  - Thyroid C-cell tumors
  - Pancreatitis
  - Diabetic retinopathy complications
  - Hypoglycemia
  - Acute kidney injury
  - Hypersensitivity

Source: Ozempic® (semaglutide). Prescribing Information. Plainsboro, NJ. 2017.

Ozempic® (semaglutide)

- **Interactions**
  - Insulin
  - Insulin secretagogues
  - Oral medications
- **Monitoring**
  - Blood glucose
  - Hemoglobin A_1C
  - Renal function
  - Signs/symptoms of pancreatitis
  - Triglycerides
- **Dosage forms available**
  - 2 mg/1.5 mL pens
    - One pen intended to administer the 0.25 mg and 0.5 mg doses
    - One pen intended to administer the 1 mg doses
- **Counseling points**
  - Never share pens between patients
  - Pens may be stored for 56 days at room temperature after opening
  - Maintain adequate hydration
  - Administer missing dose within 5 days after the missed dose

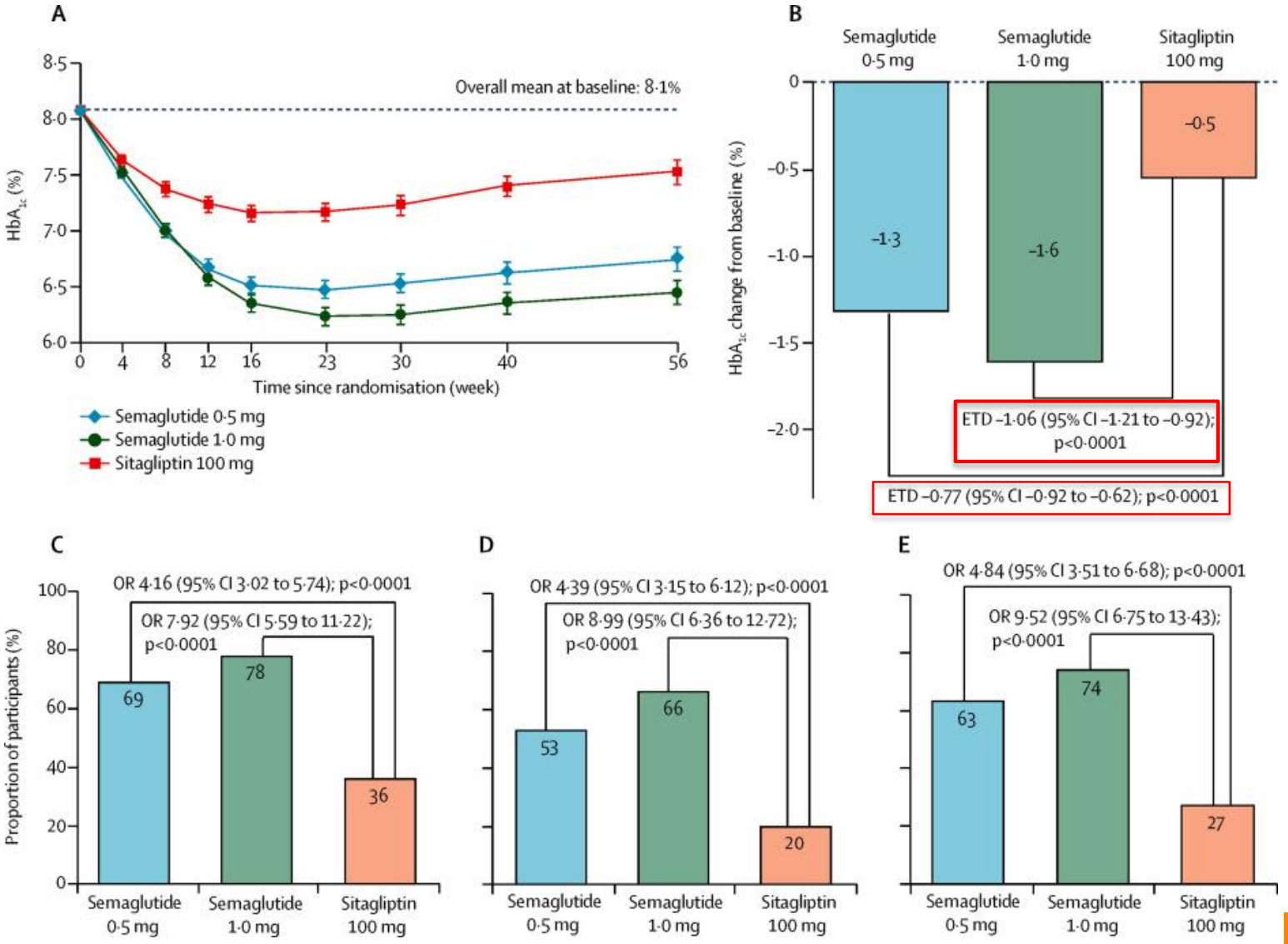
Source: Ozempic® (semaglutide). Prescribing Information. Plainsboro, NJ. 2017.

SUSTAIN 2 Trial

- Phase 3, randomized, double-blind, double-dummy, active-controlled, parallel-group, multinational, multicenter trial
  - Semaglutide 0.5 mg subcutaneously once weekly + sitagliptin PO placebo daily
  - Semaglutide 1 mg subcutaneously once weekly + sitagliptin PO placebo daily
  - Sitagliptin 100 mg PO daily + semaglutide placebo 0.5 mg subcutaneously once weekly
  - Sitagliptin 100 mg PO daily + semaglutide placebo 1 mg subcutaneously once weekly
- Primary endpoint
  - Change in mean HbA_1C concentrations from baseline to week 56
- Confirmatory secondary endpoint
  - Change in bodyweight from baseline to week 56
- Safety endpoints
  - Number of treatment-emergent adverse events
  - Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycemic episodes
  - Pulse rate
  - Occurrence and concentration of antisemaglutide antibodies

Source: Ahren B, Masmiquel L, Kumar H, et al. *Lancet Diabetes Endocrinol* 2017;5:341-54.

Results – Efficacy



Source: Ahren B, Masmiquel L, Kumar H, et al. *Lancet Diabetes Endocrinol* 2017;5:341-54.

Results – Safety

	Semaglutide 0·5 mg (n=409)		Semaglutide 1·0 mg (n=409)		Sitagliptin 100 mg (n=407)	
	Number of participants	Number of events	Number of participants	Number of events	Number of participants	Number of events
Any treatment-emergent adverse events	306 (75%)	1453	292 (71%)	1358	292 (72%)	1064
Serious adverse events	30 (7%)	55	30 (7%)	37	29 (7%)	39
Fatal adverse events*	2 (<1%)	2	1 (<1%)	1	3 (1%)	3
Severe adverse events†	26 (6%)	42	21 (5%)	31	21 (5%)	27
Moderate adverse events	122 (30%)	290	109 (27%)	300	114 (28%)	219
Mild adverse events	268 (66%)	1121	265 (65%)	1027	260 (64%)	818
Gastrointestinal adverse events	178 (44%)	462	163 (40%)	549	96 (24%)	175
Severe	13 (3%)	18	11 (3%)	17	4 (1%)	6
Moderate	56 (14%)	99	50 (12%)	132	22 (5%)	36
Mild	152 (37%)	345	144 (35%)	400	83 (20%)	133
Adverse events leading to premature discontinuation	33 (8%)	57	39‡ (10%)	70	12 (3%)	21
All gastrointestinal adverse events	27 (7%)	42	31 (8%)	51	3 (1%)	5
Nausea	11 (3%)	11	12 (3%)	15	2 (<1%)	2
Diarrhoea	10 (2%)	10	9 (2%)	9	0	..
Vomiting	3 (1%)	3	10 (2%)	10	0	..

Source: Ahren B, Masmiquel L, Kumar H, et al. *Lancet Diabetes Endocrinol* 2017;5:341-54.

Radicava® (edaravone)

- **Approval date**
  - May 2017
- **FDA approved indications**
  - Treatment of amyotrophic lateral sclerosis (ALS)
- **Mechanism of action**
  - Unknown
- **Dosing**
  - Intravenous
    - 60 mg as two consecutive 30 mg IV infusions
    - Initial: daily dosing for 14 days, then a 14-day drug-free period
    - Maintenance: daily dosing for 10 days out of 14-day periods, followed by a 14-day drug-free period
- **Adverse reactions**
  - Hypersensitivity reactions
  - Sulfite allergic reactions

Source: Radicava® (edaravone). Prescribing Information. Jersey City, NJ. 2017.

Radicava® (edaravone)

- **Interactions**
  - None
- **Monitoring**
  - Hypersensitivity reactions
- **Dosage forms available**
  - 30 mg/100 mL (0.3 mg/mL) intravenous solution
- **Counseling points**
  - Risk of hypersensitivity reactions
  - Risk of sulfite allergic reactions

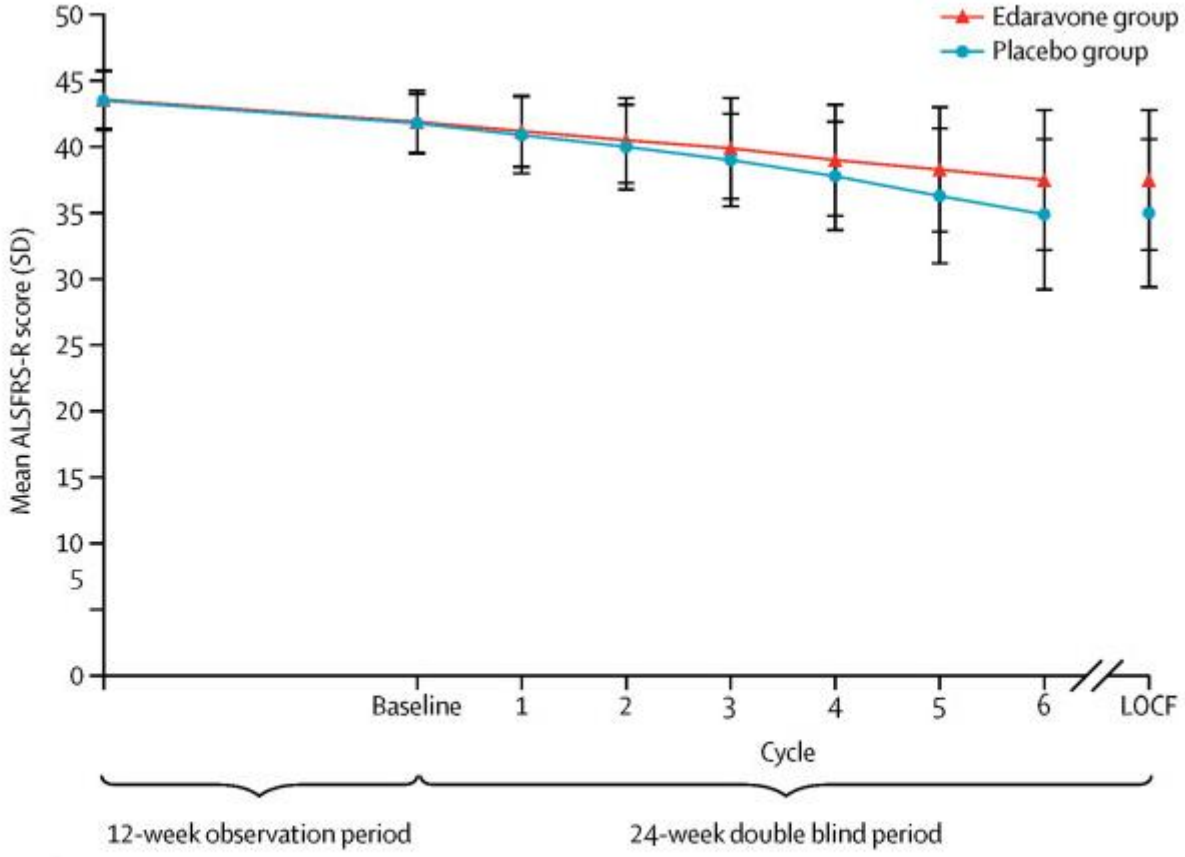
Source: Radicava® (edaravone). Prescribing Information. Jersey City, NJ. 2017.

Phase 3 Study

- Randomized, double-blind, parallel-group, placebo-controlled study
  - Edaravone 60 mg in 100 mL NS IV over 60 minutes
    - Cycle 1: 14 consecutive days, followed by 2 week drug-free period
    - Cycle 2 and thereafter: 10 days within a 14-day period, followed by a 2 week drug-free period
  - Placebo infusion
- Primary efficacy endpoint
  - Change in the Revised ALS Functional Rating Scale (ALSFRS-R) score
- Safety endpoints
  - Incidence of adverse events
  - Adverse drug reactions
  - Clinical laboratory tests
  - Sensory tests

Source: Edaravone ALS 19 Study Group. *Lancet Neurol* 2017;16(7):505-512.

Results – Efficacy



Number of participants									
Edaravone	69	69	69	67	68	68	68	68	68
Placebo	68	68	67	66	65	63	63	61	66

Source: Edaravone ALS 19 Study Group. *Lancet Neurol* 2017;16(7):505-512.

Results – Safety

	Adverse events		Serious adverse events	
	Edaravone group (n=69)	Placebo group (n=68)	Edaravone group (n=69)	Placebo group (n=68)
Any	58 (84%)	57 (84%)	11 (16%)	16 (24%)
Contusion	13 (19%)	9 (13%)	0	1 (2%)
Constipation	8 (12%)	8 (12%)	0	0
Dermatitis contact	8 (12%)	3 (4%)	0	0
Dysphagia	8 (12%)	10 (15%)	8 (12%)	8 (12%)
Eczema	5 (7%)	2 (3%)	0	0
Insomnia	5 (7%)	4 (6%)	0	0
Upper respiratory tract inflammation	5 (7%)	2 (3%)	0	0
Back pain	4 (6%)	1 (2%)	0	0
Headache	4 (6%)	5 (7%)	0	0
Myalgia	4 (6%)	1 (2%)	0	0
Nasopharyngitis	3 (4%)	5 (7%)	0	0
Respiratory disorder	3 (4%)	2 (3%)	2 (3%)	2 (3%)
Diarrhoea	2 (3%)	4 (6%)	0	0
Speech disorder	1 (1%)	2 (3%)	1 (1%)	2 (3%)
Pneumonia aspiration	0	2 (3%)	0	2 (3%)

Source: Edaravone ALS 19 Study Group. *Lancet Neurol* 2017;16(7):505-512.

Steglatro™ (ertugliflozin)

- **Approval date**
  - December 2017
- **FDA approved indications**
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
- **Mechanism of action**
  - Sodium glucose co-transporter 2 (SGLT2) inhibitor
- **Dosing**
  - Oral: 5 mg PO once daily up to max of 15 mg PO once daily
  - Renal impairment
    - eGFR 30 to 60 mL/min: not recommended to initiate or maintain
    - eGFR < 30 mL/min: contraindicated
- **Adverse reactions**
  - Hypotension
  - Ketoacidosis
  - Acute kidney injury
  - Urosepsis and pyelonephritis
  - Lower limb amputation
  - Hypoglycemia
  - Genital mycotic infections
  - Increases in low-density lipoprotein cholesterol

Source: Steglatro™ (ertugliflozin). Prescribing Information. Whitehouse Station, NJ. 2017.

Steglatro™ (ertugliflozin)

- **Interactions**
  - Insulin
  - Insulin secretagogues
  - Urine glucose tests
- **Monitoring**
  - Blood glucose
  - Hemoglobin A_1C
  - Renal function
  - Volume status
  - Cholesterol
  - Signs and symptoms of metabolic acidosis
  - Lower limb and feet sores
- **Dosage forms available**
  - 5 mg and 15 mg tablet
- **Counseling points**
  - Take with or without food
  - Monitor blood glucose
  - Maintain adequate hydration
  - Watch for signs and symptoms of ketoacidosis
  - Urine test will be positive for glucose

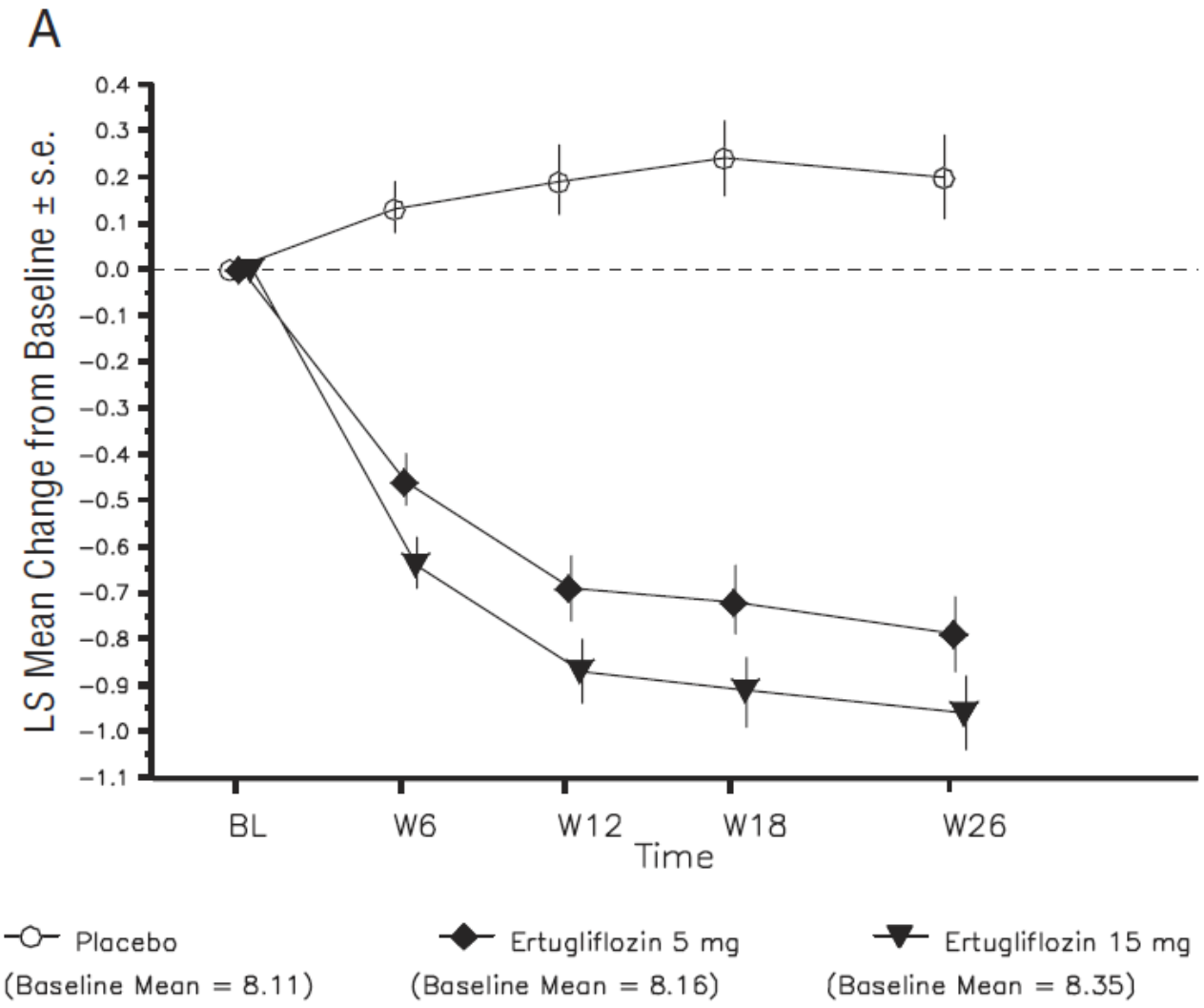
Source: Steglatro™ (ertugliflozin). Prescribing Information. Whitehouse Station, NJ. 2017.

VERTIS MONO Study

- Phase III, multicenter, randomized, parallel-group, double-blind, placebo-controlled study
  - Ertugliflozin 5 mg PO once daily in the morning
  - Ertugliflozin 15 mg PO once daily in the morning
  - Placebo PO once daily in the morning
- Primary efficacy endpoint
  - Change from baseline in HbA_1C at week 26
- Secondary efficacy endpoint
  - Proportion of participants with $HbA_1C < 7\%$ at week 26
- Safety assessments
  - Adverse event monitoring
  - Physical examination
  - Vital signs
  - Laboratory evaluations
  - EKG

Source: Terra SG, Focht K, Davies M, et al. *Diabetes Obes Metab* 2017;19:721-728.

Results – Efficacy



Source: Terra SG, Focht K, Davies M, et al. *Diabetes Obes Metab* 2017;19:721-728.

Results – Safety

	Placebo N = 153	Ertugliflozin 5 mg N = 156	Ertugliflozin 15 mg N = 152
One or more AEs (ER)	80 (52.3)	82 (52.6)	85 (55.9)
AEs related to study drug (ER)[1]	19 (12.4)	32 (20.5)	28 (18.4)
One or more serious AE (IR)	2 (1.3)	7 (4.5)	2 (1.3)
Serious AE related to study drug[1] (IR)	0	0	0
Death (IR)	0	0	0
AE leading to discontinuation of study medication (IR)	5 (3.3)	4 (2.6)	3 (2.0)
Tier 1 AEs (ER)			
Genital mycotic infection (women)	4 (5.6)	11 (16.4)[2]	14 (22.6)[2]
Genital mycotic infection (men)	1 (1.2)	3 (3.4)	5 (5.6)
Urinary tract infection	13 (8.5)	11 (7.1)	6 (3.9)
Symptomatic hypoglycaemia[3]	2 (1.3)	2 (1.3)	4 (2.6)
Hypovolaemia	6 (3.9)	2 (1.3)	3 (2.0)
Other selected AEs (ER)			
Pollakiuria	1 (0.7)	3 (1.9)	3 (2.0)
Polyuria	0	3 (1.9)	2 (1.3)
Nocturia	2 (1.3)	1 (0.6)	0
Dizziness	6 (3.9)	1 (0.6)	2 (1.3)

Source: Terra SG, Focht K, Davies M, et al. *Diabetes Obes Metab* 2017;19:721-728.

Vabomere™ (meropenem and vaborbactam)

- **Approval date**
  - August 2017
- **FDA approved indications**
  - Treatment of patients 18 years of age and older with complicated urinary tract infections (cUTI) including pyelonephritis
- **Mechanism of action**
  - Meropenem: inhibits cell wall synthesis
  - Vaborbactam: beta-lactamase inhibitor that protects meropenem from degradation by certain serine beta-lactamases such as *Klebsiella pneumoniae* carbapenemase (KPC)
- **Dosing**
  - Intravenous: 4 grams (meropenem 2 grams and vaborbactam 2 grams) IV Q8H over 3 hours
  - Renal impairment:
    - eGFR 30 to 49 mL/min: 2 g (meropenem 1 g and vaborbactam 1 g) IV Q8H over 3 hours
    - eGFR 15 to 29 mL/min: 2 g (meropenem 1 g and vaborbactam 1 g) IV Q12H over 3 hours
    - eGFR < 15 mL/min: 1 g (meropenem 0.5 g and vaborbactam 0.5 g) IV Q12H over 3 hours
- **Adverse reactions**
  - Hypersensitivity reactions
  - Seizure potential
  - *Clostridium difficile*-associated diarrhea
  - Thrombocytopenia
  - Development of drug-resistant bacteria
  - Overgrowth of nonsusceptible organisms

Source: Vabomere™ (meropenem and vaborbactam). Prescribing Information. Parsippany, NJ. 2017.

Vabomere™ (meropenem and vaborbactam)

- **Interactions**
  - Valproic acid
  - Probenecid
- **Monitoring**
  - Signs/symptoms of anaphylaxis
  - Renal function
- **Dosage forms available**
  - 2 gram vial (meropenem 1 g and vaborbactam 1 g)
- **Counseling points**
  - Risk of allergic reaction
  - Seizure potential
  - Risk for development of diarrhea

Source: Vabomere™ (meropenem and vaborbactam). Prescribing Information. Parsippany, NJ. 2017.

TANGO I Study

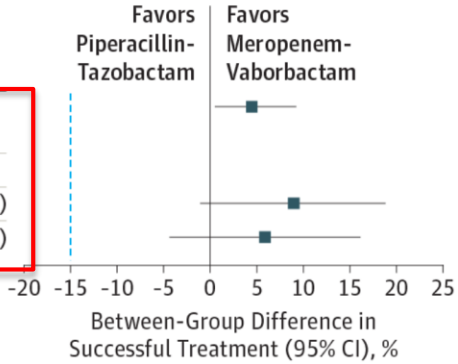
- Phase 3, multicenter, randomized, double-blind, double-dummy, active-control trial
  - Meropenem-vaborbactam 2 g/2 g IV Q8H over 3 hours
    - Drug-free saline infusion over 30 minutes
  - Piperacillin-tazobactam 4 g/0.5 g IV Q8H over 30 minutes
    - Drug-free saline infusion over 3 hours
  - After 15 doses of IV, could be switched to levofloxacin 500 mg PO Q24H
- Primary efficacy endpoint
  - FDA criteria
    - Overall success, a composite outcome of clinical cure and microbial eradication at the end of IV therapy
  - EMA criteria
    - Microbial eradication at the test-of-cure visit
- Safety
  - Adverse events

Source: Kaye KS, Bhowmick T, Metallidis S, et al. *JAMA* 2018;319(8):788-799.

Results – Efficacy

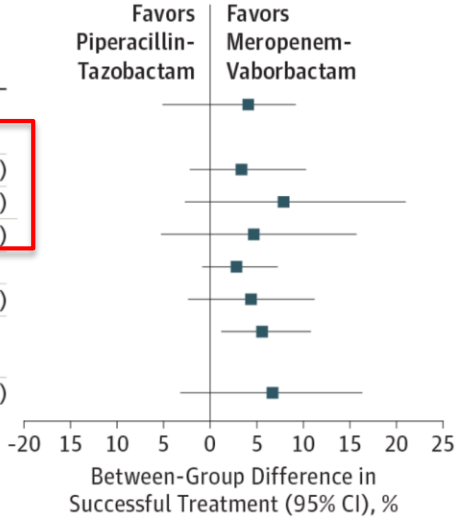
A Primary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
FDA primary: overall success at end of intravenous treatment (microbiologic MITT analysis)[a,b]	189/192 (98.4)	171/182 (94.0)	4.5 (0.7 to 9.1)
EMA primary: microbial eradication at test of cure			
Microbiologic MITT analysis[b]	128/192 (66.7)	105/182 (57.7)	9.0 (-0.9 to 18.7)
Microbiologic evaluable analysis	118/178 (66.3)	102/169 (60.4)	5.9 (-4.2 to 16.0)



B Secondary end points

	No. of Patients Successfully Treated/Total No. (%)		Between-Group Difference (95% CI), %
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	
Overall success at test of cure[a]	143/192 (74.5)	128/182 (70.3)	4.1 (-4.9 to 9.1)
Overall success at end of intravenous treatment[a]			
Acute pyelonephritis	117/120 (97.5)	95/101 (94.1)	3.4 (-2.0 to 10.2)
Complicated UTI, removable infection source[c]	35/35 (100)	35/38 (92.1)	7.9 (-2.5 to 20.9)
Complicated UTI, nonremovable infection source	37/37 (100)	41/43 (95.3)	4.7 (-5.1 to 15.6)
Clinical cure at end of intravenous treatment[d]	189/192 (98.4)	174/182 (95.6)	2.8 (-0.7 to 7.1)
Clinical cure at test of cure	174/192 (90.6)	157/182 (86.3)	4.4 (-2.2 to 11.1)
Microbial eradication at end of intravenous treatment (FDA criteria)	188/192 (97.9)	168/182 (92.3)	5.6 (1.4 to 10.7)
Microbial eradication at test of cure (FDA criteria)	132/192 (68.8)	113/182 (62.1)	6.7 (-3.0 to 16.2)



Source: Kaye KS, Bhowmick T, Metallidis S, et al. *JAMA* 2018;319(8):788-799.

Results – Safety

Table 3. Treatment-Emergent Adverse Events Occurring in 1.5% or More of Patients (Either Group; Modified Intent-to-Treat Population)[a]

Adverse Event	No. (%)[b]		
	Meropenem-Vaborbactam (n = 272)	Piperacillin-Tazobactam (n = 273)	Total (n = 545)
Headache	24 (8.8)	12 (4.4)	36 (6.6)
Diarrhea	9 (3.3)	12 (4.4)	21 (3.9)
Nausea	5 (1.8)	4 (1.5)	9 (1.7)
Asymptomatic bacteriuria	4 (1.5)	4 (1.5)	8 (1.5)
Catheter site phlebitis[c]	5 (1.8)	3 (1.1)	8 (1.5)
Infusion site phlebitis	6 (2.2)	2 (0.7)	8 (1.5)
Urinary tract infection	4 (1.5)	4 (1.5)	8 (1.5)
Hypokalemia	3 (1.1)	4 (1.5)	7 (1.3)
Vaginal infection	1 (0.4)	6 (2.2)	7 (1.3)
Alanine aminotransferase increased	5 (1.8)	1 (0.4)	6 (1.1)
Anemia	2 (0.7)	4 (1.5)	6 (1.1)
Aspartate aminotransferase increased	4 (1.5)	2 (0.7)	6 (1.1)
Pyrexia	4 (1.5)	2 (0.7)	6 (1.1)
Dyspnea	0	5 (1.8)	5 (0.9)

Source: Kaye KS, Bhowmick T, Metallidis S, et al. *JAMA* 2018;319(8):788-799.

Question 1 – Pharmacists and Technicians

Which of the following has the correct brand name matched with the correct generic name?

A. Steglatro™ (semaglutide)
B. Baxdela™ (edaravone)
C. Vabomere™ (meropenem and vaborbactam)
D. Ozempic® (ertugliflozin)

Question 1 – Pharmacists and Technicians

Which of the following has the correct brand name matched with the correct generic name?

A. Steglatro™ (semaglutide)
B. Baxdela™ (edaravone)
C. Vabomere™ (meropenem and vaborbactam)
D. Ozempic® (ertugliflozin)

ATLANTIC HEALTH SYSTEM

Question 2 – Pharmacists

The following medication works by raising blood pressure through vasoconstriction and increased aldosterone release?

A. Giapreza™ (angiotensin II)
B. Radicava® (edaravone)
C. Emflaza® (deflazacort)
D. Ozempic® (semaglutide)

Question 2 – Pharmacists

The following medication works by raising blood pressure through vasoconstriction and increased aldosterone release?

A. **Giapreza™ (angiotensin II)**
B. Radicava® (edaravone)
C. Emflaza® (deflazacort)
D. Ozempic® (semaglutide)

Question 3 – Pharmacists

The following medication has a black box warning for tendinitis and tendon rupture

A. Brineura™ (cerliponase alfa)
B. Emflaza® (deflazacort)
C. Giapreza™ (angiotensin II)
D. Baxdela™ (delafloxacin)

Question 3 – Pharmacists

The following medication has a black box warning for tendinitis and tendon rupture

A. Brineura™ (cerliponase alfa)
B. Emflaza® (deflazacort)
C. Giapreza™ (angiotensin II)
D. Baxdela™ (delafloxacin)

Question 4 – Pharmacists and Technicians

Unlike other medications in its class, Ozempic® (semaglutide) pens may be stored for ___ days after they are removed from the refrigerator.

A. 14 days
B. 30 days
C. 56 days
D. 60 days

Question 4 – Pharmacists and Technicians

Unlike other medications in its class, Ozempic® (semaglutide) pens may be stored for ___ days after they are removed from the refrigerator.

A. 14 days
B. 30 days
C. 56 days
D. 60 days

ATLANTIC HEALTH SYSTEM

Question 5 – Pharmacists

Patient counseling for which of the following medications should include that their urine will test positive for glucose due to the mechanism of action of the medication.

A. Ozempic® (semaglutide)
B. Steglatro™ (ertugliflozin)
C. Giapreza™ (angiotensin II)
D. Vabomere™ (meropenem and vaborbactam)

Question 5 – Pharmacists

Patient counseling for which of the following medications should include that their urine will test positive for glucose due to the mechanism of action of the medication.

A. Ozempic® (semaglutide)
B. Steglatro™ (ertugliflozin)
C. Giapreza™ (angiotensin II)
D. Vabomere™ (meropenem and vaborbactam)

FDA Updates 2017

ATLANTIC HEALTH SYSTEM

Atlantic Health System

Codeine and Tramadol Medicines: Restricting Use

- April 20th, 2017
- FDA is restricting the use of codeine and tramadol medicines in children
  - Codeine and tramadol now contraindicated in children less than 12 years of age
  - Tramadol is now contraindicated in children less than 18 years of age to treat pain after surgery to remove the tonsils and/or adenoids
  - Recommendation against their use in adolescents between 12 and 18 years of age
  - Recommendation against their use in breastfeeding mothers
- Recommendation
  - Prescribers
    - Codeine and tramadol are only FDA approved for use in adult patients
    - Use over-the-counter alternatives or other FDA approved prescription medications
  - Pharmacists
    - Review pediatric medication profiles for the use of codeine and tramadol and recommend alternatives, if necessary
  - Patients
    - Read labels on prescription bottles and talk to healthcare professional to ensure that child's medication does not contain codeine or tramadol

Source: FDA Drug Safety Communication: Codeine and Tramadol Medicines: Drug Safety Communication – Restricting Use in Children, Recommending Against Use in Breastfeeding Women. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Accessed July 17, 2018.

General Anesthetic and Sedation Drugs: Label Changes in Young Children

- April 27th, 2017
- FDA has approved new warning stating that exposure to these medicines for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years
  - Studies in animals suggested that anesthetic and sedation drugs for more than 3 hours can cause widespread loss of nerve cells in the developing brain
    - Long-term negative effects on the animals' behavior or learning
- Recommendation
  - Prescribers
    - Continue to counsel patients on risks and benefits of surgery and anesthesia
    - Surgeries or procedures in children younger than 3 years should not be delayed or avoided when medically necessary
    - Elective surgeries could potentially be delayed if medically appropriate
  - Pharmacists
    - Provide necessary counseling to patients regarding risks
  - Patients
    - Talk to healthcare professionals if they have questions or concerns about general anesthesia and sedation medications

Source: FDA Drug Safety Communication: General Anesthetic and Sedation Drugs: Drug Safety Communication – FDA Approves Label Changes for Use in Young Children. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm554634.htm. Accessed July 17, 2018.

Kayexalate: Separate Dosing

- September 6th, 2017
- FDA recommends patients avoid taking the potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) at the same time as other medicines taken by mouth
  - Can decrease absorption and therefore effectiveness of these other medications
- Recommendation
  - Prescribers
    - Advise patients to separate dosing from other orally administered medications by at least 3 hours
  - Pharmacists
    - Counsel patients to separate dosing
  - Patients
    - Take orally administered prescription and over-the-counter medications at least 3 hours before or 3 hours after taking Kayexalate

Source: FDA Drug Safety Communication: Kayexalate (sodium polystyrene sulfonate): Drug Safety Communication – FDA Recommends Separating Dosing. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm572484.htm. Accessed July 17, 2018.

Ocaliva (obeticholic acid): Increased Risk of Serious Liver Injury

- September 21st, 2017
- FDA is warning that patient with moderate to severe decreases in liver function are being incorrectly dosed and this is increasing the risk of serious liver injury and death
- Recommendation
  - Prescribers
    - Patient with severe liver impairment (Child-Pugh B and C) should be started on a dose of 5 mg once weekly and maybe increased to maximum dose of 10 mg twice weekly
    - Monitor patients for disease progression and reduce dose from daily to weekly as liver function declines
    - Educate patients on symptoms of potential liver injury
  - Pharmacists
    - Ensure correct dosing based on patient's liver function
  - Patients
    - Report new or worsening severe skin itching
    - Contact healthcare professional if develop symptoms of potential liver injury

Source: FDA Drug Safety Communication: Ocaliva (obeticholic acid): Drug Safety Communication – Increased Risk of Serious Liver Injury. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm576656.htm. Accessed July 17, 2018.

Uloric (febuxostat): Increased Risk of Heart-Related Death

- November 15th, 2017
- FDA is warning public that preliminary results from a safety study have shown increased risk of heart-related death with febuxostat (Uloric) compared to allopurinol
- Recommendation
  - Prescribers
    - Consider this safety information when deciding whether to prescribe or continue patients on febuxostat
  - Pharmacists
    - Counsel patients on potential adverse effects of the medication
  - Patients
    - Talk to healthcare professional about any concerns
    - Do not stop taking medication without first consulting with a healthcare professional

Source: FDA Drug Safety Communication: Uloric (febuxostat): Drug Safety Communication – FDA to Evaluate Increased Risk of Heart-Related Death. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm584702.htm . Accessed July 17, 2018.

Long-Acting Beta Agonists (LABAs) and Inhaled Corticosteroids (ICS): Boxed Warning About Asthma-Related Death Removed

- December 20th, 2017
- FDA has removed the boxed warning about asthma-related death from the labels of medicines that contain both an ICS and LABA
- Recommendation
  - Prescribers
    - Refer to the most recently approved drug labels for recommendations on using ICS/LABA medicines
  - Pharmacists
    - Counsel patients on proper use of their inhalers
  - Patients
    - Talk to healthcare professional about any concerns
    - Do not stop taking medication without first consulting with a healthcare professional

Source: FDA Drug Safety Communication: Long-Acting Beta Agonists (LABAs) and Inhaled Corticosteroids (ICS): Drug Safety Communication – Boxed Warning About Asthma-Related Death Removed. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm589587.htm. Accessed July 17, 2018.

Conclusion

- In 2017 …
  - 46 novel drugs approved
    - 15 first in class
    - 18 to treat rare diseases
  - 12 new medications for cancer
  - 6 new medications to treat infectious diseases
  - 2 new medications to treat type II diabetes
  - Multiple FDA updates

Question 6 – Pharmacists and Technicians

The following medication is now contraindicated in patients less than 12 years of age

A. Codeine
B. Kayexalate® (sodium polystyrene sulfonate)
C. Ocaliva® (obeticholic acid)
D. Uloric™ (febuxostat)

Question 6 – Pharmacists and Technicians

The following medication is now contraindicated in patients less than 12 years of age

A. **Codeine**
B. Kayexalate® (sodium polystyrene sulfonate)
C. Ocaliva® (obeticholic acid)
D. Uloric™ (febuxostat)

Question 7 – Technicians

Which of the following medications must be prepared using aseptic technique and then dispensed in sterile packaging since it will be administered into the ventricle?

A. Emflaza® (deflazacort)
B. Radicava ® (edaravone)
C. Baxdela™ (delafloxacin)
D. Brineura™ (cerliponase alfa)

Question 7 – Technicians

Which of the following medications must be prepared using aseptic technique and then dispensed in sterile packaging since it will be administered into the ventricle?

A. Emflaza® (deflazacort)
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C. Baxdela™ (delafloxacin)
D. Brineura™ (cerliponase alfa)

New Medications and FDA Updates 2017

Suzannah Kokotajlo, PharmD
Suzannah.Kokotajlo@AtlanticHealth.org

ATLANTIC HEALTH SYSTEM

Atlantic Health System