Emerging Trends: Top 10 New Drugs

OBJECTIVES:
1. IDENTIFY THE TOP TEN NEW DRUGS.
2. DESCRIBE EACH DRUG'S ROLE IN THERAPY.

Learning Assessment
Who is the primary patient population that is affected by Duchenne Muscular Dystrophy?
A. Males and females > 20 years old
B. Males ~3-5 years old
C. Females ~3-5 years old
D. All genders and all ages

Speaker Disclosure
Maren Beckman has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
Indicated for the treatment of Duchenne muscular dystrophy (DMD)
No unapproved uses at this time

Duchenne Muscular Dystrophy (DMD)
Genetic disorder characterized by progressive muscle degeneration
Caused by absence of dystrophin
- Protein that keeps muscle cells intact
Early onset (3-5 years old), primarily boys
Usually first affects hips, pelvic area, thighs, and shoulders, then moves to arms, legs, and trunk
- Early teens: respiratory and heart muscles affected
**Formulation**

- **Oral tablet**
  - 6 mg, 18 mg, 30 mg, and 36 mg
- **Oral suspension**
  - 22.75 mg/mL

**Mechanism of Action**

Corticosteroid prodrug

Active metabolite (21-desacytyleflazacort) acts on glucocorticoid receptor to exert anti-inflammatory and immunosuppressive effects

Unknown MOA in DMD patients

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**Pharmacokinetics**

**Absorption**
- Fasted state: peak concentrations ~1 hour
- High fat meal reduces absorption ~30% and delays peak concentrations by 1 hour

**Distribution**
- 40% bound to human plasma proteins

**Metabolism**
- Converted to active 21-desDFZ by esterases, further metabolized by CYP 3A4 to inactive metabolites

**Excretion**
- Eliminated by kidney (~68% of dose)
- Almost full elimination 24 hours post-dose

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**Dosing**

Recommended: 0.9 mg/kg/day
- Round up to nearest possible dose
- Any combination of four tablet strengths can be used to achieve dose
- Round up to nearest tenth of milliliter (mL) when using suspension

Max dose: 0.9 mg/kg/day

Titration down necessary if used for more than a few days

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**Special Populations**

**Pregnant/Nursing**
- Corticosteroids should only be used if potential benefits outweigh the potential risks to the fetus
- Nursing: appears in human milk and could suppress growth and have other adverse effects

**Pediatric**
- Approved for pediatrics 5 years of age and older

**Geriatric**
- Not applicable
Special Populations

Hepatic Impairment
- No dose adjustment necessary in mild or moderate hepatic impairment
- No clinical experience with severe impairment

Renal Impairment
- No dose adjustment necessary

Contraindications

Any patient with known hypersensitivity to drug or any inactive component
Suspension contains benzyl alcohol so should not use in patient with known hypersensitivity

Precautions

May mask symptoms of infections
Monitor for alterations in endocrine function
Congestive heart failure, hypertension, renal disease
Increased risk of GI perforation
Use with caution in patients with psychosis or emotional instability
Growth inhibition in pediatrics

Adverse Reactions

Most common
- Cushingoid appearance
- Increased weight, appetite
- Polyuria
- Upper respiratory tract infection, cough
- Hirsutism
- Central obesity
- Nasopharyngitis

More severe
- Hepatitis B reactivation
- Infections
- Severe psychiatric adverse reactions (euphoria, insomnia, mood swings)
- Avascular necrosis
- Toxic epidermal necrolysis
- Increased risk of thromboembolism

Drug-Drug Interactions

Moderate or strong 3A4 Inhibitors
- Give 1/3 of recommended dosage of Emflaza

Moderate or strong 3A4 Inducers
- Avoid concomitant use of Emflaza
Price
List drug price as wholesale acquisition cost (WAC).
- Suspension (13 mL): $2,873.00
- 6 mg tabs (100): $4,361.00
- 18 mg tabs (30): $3,925.00
- 30 mg tabs (30): $6,542.00
- 36 mg tabs (30): $7,290.00

Place in therapy
Treatment for patients 5 years of age or older with DMD
Orphan drug status in the United States
Choose between prednisone or Emflaza
- Emflaza: last line therapy

Additional information
Tablets
- May be taken without regards to meals
- May crush into applesauce and immediately taken
Suspension
- May be given without regards to meals
- Shake well
- After withdrawing appropriate dose, slowly add to 3-4 oz of juice or milk and mix well
- Administer immediately and consume entirety
- Bottle should be discarded after opening
Should not be discontinued abruptly

Learning Assessment
Who is the primary patient population that is affected by Duchenne Muscular Dystrophy?
A. Males and females > 20 years old
B. Males ~3-5 years old
C. Females ~3-5 years old
D. All genders and all ages

References
Speaker Disclosure
Juan Castro has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Learning Assessment
The most common adverse effects associated with Eucrisa therapy include (select all that apply):
A. Site pain
B. Redness
C. Swelling
D. Hives
E. Hypersensitivity reactions

Indication
FDA Approved Indication:
◦ For the treatment of mild to moderate atopic dermatitis in adults and children 2 years of age and older
FDA press release December 14, 2016
Currently no unapproved uses

Atopic Dermatitis: Overview
A disorder by many names
◦ Atopic dermatitis (American Academy of Dermatology)
◦ Eczema (most common term)
◦ Atopic eczema, dermatitis
10-20% of children, 1-3% of adults worldwide
◦ 90% before age 5 of those who get it
Causes: unknown
◦ Not contagious, runs in families

Atopic Dermatitis: Children
Appears in the creases of elbows and knees
◦ Neck, wrists, ankles, and leg/buttocks creases also common
◦ Itchy scaly patches
In time
◦ Patches get bumpy
◦ Can lighten, darken, or thicken (turn leathery)
◦ Can develop knots
◦ Constant itching
**Atopic Dermatitis: Adults**

- Creases of elbows, knees, nape of neck
- Covers much of the body
- Especially noticeable in neck and face, especially in the eyes
- Dry, scaly, non-stop itchy skin
  - Can lead to infections

**Mechanism of Action**

- Not fully defined
- Been found to increase cAMP by inhibiting PDE-4
- Leads to a downstream decrease in the production of inflammatory cytokines

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**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>97% plasma protein bound</td>
<td></td>
</tr>
</tbody>
</table>

- Metabolism
  - Highly metabolized into 2 inactive metabolites
- Excretion
  - Both metabolites primarily excreted through the kidneys

- Time to steady state: 8 days
- No laboratory monitoring necessary

**Dosing**

- Apply a thin layer to the affected area(s) twice daily
- Special populations
  - Pediatric (2 years and up) & geriatric
  - The same as adult dosing
  - No hepatic or renal adjustments
  - No or limited data on use during pregnancy or breastfeeding

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**Contraindications**

- Hypersensitivity to Eucrisa or any components of the formulation

**Precautions**

- For topical dermatologic use only
  - Not ophthalmic, oral, or vaginal administration
Adverse Reactions

The most common:
- Site pain
- Hives

The most severe:
- Hypersensitivity reactions

Drug-Drug Interactions

None reported

Affected by CYP1A2, CYP2B6, CYP2C8, and CYP2C9 enzymes

Price

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Wholesale Acquisition Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>2% Cream, 60 grams</td>
<td>$580</td>
</tr>
</tbody>
</table>

Place in therapy

Treatment for atopic dermatitis largely consists of lifestyle modifications
No cure exists, but is self-limiting, and outcomes are better if it develops in an infant or child
Medicines, including Eucrissa, are prescribed as needed to manage symptoms

Learning Assessment

The most common adverse effects associated with Eucrissa therapy include (select all that apply):

A. Site pain
B. Redness
C. Swelling
D. Hives
E. Hypersensitivity reactions

The most common adverse effects associated with Eucrissa therapy include (select all that apply):

A. Site pain
B. Redness
C. Swelling
D. Hives
E. Hypersensitivity reactions (not common but may be serious)
Learning Assessment

The most severe adverse effect associated with Eucrisa therapy include (select all that apply):

A. Site pain
B. Redness
C. Swelling
D. Hives
E. Hypersensitivity reactions

References

Learning Assessment
What type of molecule is eteplirsen, and by what mechanism does it modify the dystrophin protein?
A. Oligosaccharide; inhibits metabolism
B. Oligopeptide; inhibits protein formation
C. Oligonucleotide; causes mutated exon exclusion
D. Small molecule; enzyme inhibition

Speaker Disclosure
Kristen Guilianohas no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
FDA approved for:
◦ Treatment of Duchenne Muscular Dystrophy in patients with a confirmed mutation in the DMD gene amendable to exon 51 skipping.

Duchenne Muscular Dystrophy
Caused by dystrophin gene mutations
◦ Defective X-chromosome gene, mostly deletions in exon(s)
Pathologic process is characterized by muscular fiber degeneration
◦ Dystrophin reinforces the sarcolemma, stabilizing the glycoprotein complex and preventing breakdown by proteases
Marked by weakness in the patient
◦ Proximal muscles before distal, lower limbs before upper limbs

Drug Formulation
Exondys 51 is supplied in single-dose vials of 100 mg/2 mL and 500 mg/10 mL (both 50 mg/mL)
Exondys 51 is administered via IV infusion over 35-60 minutes
Flush IV line with normal saline before and after infusion
Do not mix other medications with Exondys 51 or infuse other medications concomitantly via the same IV access line
Mechanism of Action

Antisense oligonucleotide

Binds to exon 51 of dystrophin pre-mRNA, leading to exclusion of this exon during mRNA processing (in patients with mutations receptive to exon 51 skipping)

Skipping exon 51 allows for assembly of internally truncated dystrophin protein

Pharmacokinetics

Absorption
- Peak plasma concentrations occurred near the end of infusion

Distribution
- Plasma protein binding ranges between 6 to 17%
- The average apparent volume of distribution (Vss) was 600 mL/kg

Pharmacokinetics

Metabolism
- Not hepatically metabolized

Excretion
- Two-thirds of the dose is renally eliminated in 24 hours
- Half-life (t1/2) is 3 to 4 hours

Dosing

Normal/Maintenance Dose
- The recommended dose is 30 mg/kg given once weekly as a 35-60 minute IV infusion.
- If a dose is missed, it may be administered as soon as possible after the scheduled time.

Special Populations

Pregnant/Nursing
- No human or animal data available

Geriatric
- Not studied

Hepatic and Renal Impairment
- Not studied

Special Populations

Pediatric
- IV use of eteplirsen in rats resulted in renal tubular necrosis at high doses and decreased bone density parameters at all doses
- Kidney damage was marked by increased BUN/SCr and decreased CrCl
- No effects on male reproductive system, neurobehavioral development, or immune function
Contraindications and Precautions

No contraindications have been identified.
No precautions have been identified.

Adverse Reactions

The most common: balance disorder and vomiting
Infusion-associated: increased body temperature, erythema.

Drug-Drug Interactions

No drug-drug interactions have been identified.
Eteplirsen does not significantly inhibit or induce any of the CYP enzymes or impact protein binding or drug transporters

Price

Wholesale Acquisition Cost
- 100 mg/2 mL (2 mL): $1,600.00
- 500 mg/10 mL (10 mL): $8,000.00

Place in therapy

All DMD patients are initially treated with glucocorticoids (prednisone or deflazacort).
Clinical benefit of eteplirsen has not been established
Further approval from the FDA relies on more clinical trials

Additional information

Anything extra that the pharmacist/patient should know?
- Consider using a topical anesthetic during infusion.
- Transient erythema, facial flushing, and elevated temperature possible with infusion

Patient Counseling tips
- Patient may experience vomiting, bruising, excoriation, arthralgia, rash, catheter site pain, and upper respiratory tract infection
Learning Assessment

What type of molecule is eteplirsen, and by what mechanism does it modify the dystrophin protein?

A. Oligosaccharide; inhibits metabolism
B. Oligopeptide; inhibits protein formation
C. Oligonucleotide; causes mutated exon exclusion
D. Small molecule; enzyme inhibition

References

Exondys 51 (eteplirsen) [prescribing information]. Cambridge, MA; Sarepta Therapeutics, Inc: September 2016.

Darras, BT. Clinical features and diagnosis of Duchenne and Becker muscular dystrophy. UpToDate.

Learning Assessment

One of the most common adverse effects associated with Prasterone (Intrarosa) is:

A. Vaginal Discharge
B. Hyperglycemia
C. Mood changes
D. Nausea/Vomiting

Speaker Disclosure

Austin Hansen has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication

FDA approval for:
- for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

FDA approval date:
- November 16, 2016

Dyspareunia

Menopause:
- decline in both androgens and estrogens in women

Result in vulvovaginal atrophy:
- Thinning of vaginal wall
- Decrease in vaginal lubrication and elasticity
- Resulting in dyspareunia
- Pain during sexual activity

Drug Formulation

Vaginal Insert
- Bullet shaped smooth insert
Mechanism of Action

Prasterone
- Dehydroepiandrosterone (DHEA)
Inactive endogenous steroid converted to:
- Active androgens and/or estrogens
- Local replacement of sex steroids with minimal systemic exposure

Pharmacokinetics

Absorption/Distribution
- Designed for local administration
- Higher serum levels of prasterone, testosterone, and estradiol compared to placebo
- Levels were still considered within normal limits

Metabolism
- Enzymes: hydroxysteroid dehydrogenases, 5α-reductases, aromatases
- Active metabolites: estradiol and testosterone

Excretion
- Vaginal Discharge

Dosing

6.5 mg of prasterone
- Once daily at bedtime
- Using supplied applicator

Special Populations

Pregnant/Nursing
- Only indicated in postmenopausal women

Hepatic Impairment
- Has not been studied

Renal Impairment
- Has not been studied

Contraindications

Undiagnosed abnormal genital bleeding

Precautions

Current/History Breast cancer
- Estrogen is a metabolite of prasterone
- Estrogen contraindicated in breast cancer

Hazardous agent
- Meets NIOSH 2016 criteria
Adverse Reactions
The most common:
* Vaginal Discharge (6-14%)
* Accredited to fat vehicle of insert
* Abnormal Pap Smear (2%)

Drug-Drug Interactions
No major drug interactions

Price
Wholesale acquisition cost (WAC)
* 28-insert Pack: $175.00

Place in therapy
Current Therapy:
* Intravaginal moisturizers and lubricants
* Estrogen therapy
* Local estrogen for patients with vaginal symptoms only
* Moderate/severe dyspareunia:
* Ospemifene: Oral SERM

Place in Therapy
Potential advantages:
* Local administration
* Less risk of drug/drug interactions
* Less systemic exposure to exogenous steroids
* Less adverse effects
* Potential for less cardiovascular risk
* Estrogens: venous thromboembolism, stroke

Additional information
Supplied as a box of blister packs
* Contains 28 inserts

Patient Counseling tips:
* Adverse effects:
  * Vaginal Discharge
  * Abnormal Pap Smear
  * Intravaginal use only
* Review instructions for use in package insert
Learning Assessment

One of the most common adverse effect associated with Intrarosa is:
A. Vaginal Discharge
B. Hyperglycemia
C. Mood changes
D. Nausea/Vomiting

References

Intrarosa (prasterone) [prescribing information]. Quebec City, Canada: Endoceutics Inc; November 2016.


**Learning Assessment**

The most common adverse effects associated with Lartruvo therapy include (select all that apply):

a) Musculoskeletal pain  
b) Fatigue  
c) Nausea  
d) Hyperkalemia  
e) Hypoglycemia

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**Indicator**

**FDA approved for:**

- Treatment of soft tissue sarcoma not amenable to curative treatment with surgery or radiotherapy, in combination with doxorubicin.

**FDA approved October 19, 2016 (accelerated approval)**

Currently no unapproved uses

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**Soft Tissue Sarcoma (STS)**

A malignant tumor that develops from soft tissues such as fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues.

Found in any part of the body yet most are seen in the arms, legs, trunk, and retroperitoneum.

- There are numerous subtypes of STS with the most common being leiomyosarcoma (LMS) and liposarcoma.

**Prognostic Factors**

- Patient’s age
- Size, sarcoma subtype, histologic grade, mitotic activity, and stage of tumor

**Soft Tissue Sarcoma (continued)**

Factors with a poorer prognosis:

- Older than 60 years of age
- Tumors larger than 5 cm in greatest dimension
  - High-grade histology with high mitotic activity
  - Positive margins after resection

12,390 new cases and 4,990 deaths are expected in the U.S. in 2017
Mechanism of Action

Human IgG1 monoclonal antibody that binds the platelet-derived growth factor receptor-alpha (PDGFR-alpha)

- Prevents binding of PDGF-AA, –BB, and –CC ligands, blocks receptor activation, and disrupts PDGF receptor signaling
- PDGF-alpha receptor plays a role in cell differentiation, growth, and angiogenesis

Pharmacokinetics

Administered intravenously

Volume of distribution at steady-state (Vss) is 7.7 L
Mean clearance: 0.56 L/day
No dependence on CYP-mediated metabolism
Elimination primarily by IgG breakdown
Estimated elimination half-life: 11 days (range 6-24 days)

Dosing

Adults: 15 mg/kg IV over 60 minutes on days 1 and 8 repeated every 21 days until disease progression or unacceptable toxicity
- In combination with IV doxorubicin 75 mg/m² on day 1, repeated every 21 days for up to 8 cycles
- On day 1 of cycle 1, premedicate with diphenhydramine (25 to 50 mg IV) and dexamethasone (10 to 20 mg IV) prior to Lartruvo administration

Maximum dose for adults/geriatric: 15 mg/kg IV

Special Populations

Pediatric/Adolescents
- Safety and efficacy not established

Hepatic Impairment
- No dosage adjustments in manufacturer's labeling however, mild to moderate impairment has no clinically relevant impact on PK and has not been studied in severe impairment (total bilirubin above 3x upper limit of normal)

Renal Impairment
- No dosage adjustments in manufacturer's labeling however, mild to moderate impairment has no clinically relevant impact on PK and has not been studied in CrCl <30 mL/min

Pregnancy Implications

Females of Reproductive Potential
- Utilize adequate contraception during therapy and 3 months following therapy

Breast-Feeding Considerations
- Not known if excreted into breast milk yet due to potential for serious adverse reactions, it is not recommended to breast-feed during therapy and for 3 months following the last dose

Contraindications

None
Precautions

GI toxicity
• Nausea, vomiting, diarrhea, mucositis, abdominal pain
• Higher incidence than with doxorubicin therapy alone

Infusion reaction
• Most occur within the 1st or 2nd cycle
• Symptoms: flushing, dyspnea, bronchospasm, fever/chills
• Premedicate with diphenhydramine and dexamethasone

Hematologic toxicity
• Higher incidence of grade 3 or 4 lymphopenia and neutropenia

Adverse Reactions

The most common:
◦ Nausea (73%)
◦ Fatigue (69%)
◦ Mucositis (53%)  
◦ Alopecia (52%)
◦ Musculoskeletal pain (64%)
◦ Hyperglycemia (52%)
◦ Hypokalemia (21%)
◦ Hypophosphatemia (21%)
◦ Hypomagnesemia (16%)

Adverse Reactions (continued)

The most severe:
◦ Neuropathy (22%)
◦ Increased serum alkaline phosphatase (16%)
◦ Lymphocytopenia (77%)
◦ Neutropenia (65%)
◦ Thrombocytopenia (63%)
◦ Prolonged partial thromboplastin time (33%)

Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Interacting Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG (Intravesical)</td>
<td>Myelosuppressive Agents may diminish the therapeutic effect of BCG. AVOID.</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Myelosuppressive Agents may enhance the adverse/toxic effect of Clozapine. The risk of neutropenia may be increased. MONITOR.</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. AVOID.</td>
</tr>
</tbody>
</table>

Price

Wholesale Acquisition Cost
◦ Solution (Intravenous)
  • 190 mg/19 mL (19 mL): $896.80
  • 500 mg/50 mL (50 mL): $2,360.00

Place in therapy

Indicated in combination with doxorubicin in patients who are not susceptible to curative treatment with radiotherapy or surgery; the role of chemotherapy in soft tissue sarcoma is not well defined

For treatment of adult patients with STS who have a histologic subtype for which an anthracycline-containing regimen would be appropriate

In one study, progression-free survival increased with combination of olaratumab plus doxorubicin versus doxorubicin alone
Additional information

Protect from light
Do not freeze
Refrigerate (between 36 and 46 degrees F)
Do not give as an IV push or bolus; flush the IV line with normal saline at the end of infusion
Monitoring Parameters: CBC with differential and monitor for signs/symptoms of infusion reactions
Meets criteria for hazardous drug

Learning Assessment

The most common adverse effects associated with Lartruvo therapy include (select all that apply):

a) Musculoskeletal pain
b) Fatigue
c) Nausea
d) Hyperkalemia
e) Hypoglycemia

References

Learning Assessment
Some potential disease states that could potentially interact with Rhofade include (select all that apply):

- a) End Stage Renal Disease
- b) Cardiovascular disease
- c) Vascular insufficiency
- d) Narrow angle glaucoma

Indication
Topical treatment of persistent facial erythema associated with rosacea in adults
FDA approved January 19, 2017
Currently no unapproved uses

Rosacea
Redness that spreads from face to the trunk of the body
- Starts with tendency to blush or flush more frequently (cheeks & nose)
- Spread to forehead, chin, ears, chest, and back

Other signs and symptoms can occur
As time progresses, people can often see permanent redness in the center of their face

Rosacea (continued)
Four subtypes:
- Erythematotelangiectatic rosacea: Redness, flushing, visible blood vessels
- Papulopustular rosacea: Redness, swelling, acne-like breakouts
- Phymatous rosacea: skin thickens & bumpy texture
- Ocular rosacea: eyes are red & irritated, eyelids may become swollen; may look like sty

Speaker Disclosure
Kimberly Leong has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.
Rosacea (continued)

Possible causes:
- Hereditary
- Bacillus oleronis
- H. pylori
- Demodex
- Cathelicidin

More than 14 million people are living with rosacea in the U.S.
No cure

Other treatments for rosacea

- Sunscreen daily
- Emollient
- Lasers or light treatments
- Antibiotics
- Dermatologists can remove thickened skin
  - Lasers
  - Dermabrasion
  - Electrocautery

Mechanism of Action

Relatively selective alpha 1A adrenoceptor agonist
- Direct vasoconstriction

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Topically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>56.7% - 57.5% plasma protein bound</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Minimal metabolism (hepatic)</td>
</tr>
<tr>
<td>Excretion</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Dosing

Initial
- Pea sized amount once daily

Special populations
- Pediatric: Not established in patients below age 18 years old
- No dosage adjustments for hepatic & renal impairment

Administration

Topical use only

Before using, prime pump several times until cream is dispensed.
Pump 3 more times onto tissue & discard tissue
Tube does not require priming
Apply smoothly & evenly as thin layer across face; avoid lips & eyes
Do not apply to irritated skin or open wounds
Wash hands immediately after applying
Precautions

Cardiovascular disease
- May affect blood pressure
- Caution with uncontrolled cardiovascular disease, orthostatic hypotension and uncontrolled hypertension or hypotension
- May potentiate vascular insufficiency
- Caution with cerebral or coronary insufficiency, scleroderma, thromboangiitis obliterans, & Raynaud phenomenon

May increase risk of angle closure glaucoma in patients with narrow-angle glaucoma
Caution in patients with Sjogren syndrome

Adverse Reactions

Dermatologic
- Exacerbation of acne rosacea

Local
- Application site dermatitis
- Application site erythema
- Application site pain

Drug-Drug Interactions

Alpha 1 adrenergic receptor antagonist
Monoamine oxidase inhibitors

Storage

Store at 20-25 degrees C (68-77 degrees F)
Store in a dry area
Keep all medications out of reach of children & pets

Price

Wholesale Acquisition Cost
- 1% cream (30gm) = $75.00
No generics available

Place in therapy

Use in adults that have persistent facial redness due to rosacea that has not been able to be treated with other medications
Additional information

Do not use Rhofade on other people even if they have similar symptoms.

Rhofade has not been studied for any other indication other than persistent facial redness due to rosacea. Do not use it for other conditions.

Rhofade pumps need to be primed before initial use. Rhofade tubes do not need to be primed.

Wash hands immediately after applying cream.

Learning Assessment

Some potential disease states that could potentially interact with Rhofade include (select all that apply):

- a) End Stage Renal Disease
- b) Cardiovascular disease
- c) Vascular insufficiency
- d) Narrow angle glaucoma

References


Learning Assessment

Rucaparib is FDA approved for the treatment of advanced ovarian cancer with which mutation?

A. p53  
B. BRCA 1/2  
C. BCR-ABL1  
D. BRAF V600

Speaker Disclosure

Lauren Pohren has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication

FDA approved indication: Ovarian cancer, advanced

- Monotherapy treatment of deleterious BRCA mutation (germline and/or somatic) in advanced ovarian cancer in patients who have been treated with 2 or more chemotherapies
- No unapproved uses at this time

Ovarian Cancer

Gynecological cancer that often arises from disruptions or mutations in the epithelium of the ovary

- Associated with the highest mortality of gynecological cancers
- Most patients present with advanced disease and have a 5-year survival rate of 10% to 30%

Initial Therapy

Standard Therapy:

- Cytoreductive surgery
- Adjuvant chemotherapy
- Approximately 70% of patients achieve initial complete response to therapy
- >50% of patients will have recurrence within 2 years of therapy
Treatment of Progressive Disease

No standard therapy for reoccurrence

Management of reoccurrence stratified by platinum-free interval (PFI)
- < 6 months of platinum therapy: platinum resistant
- Progression while on platinum therapy: platinum refractory
- ≥ 6 months of platinum therapy: platinum sensitive

PARP Inhibitors

BRCA genes are tumor suppressor genes that encode proteins involved in DNA repair
Poly-ADP ribose polymerase (PARP) inhibitors have activity in BRCA + ovarian cancer
PARP enzymes are involved DNA repair
- Blocking PARP enzymes can result in DNA damage apoptosis, and decreased tumor growth or shrinkage

Mechanism of Action

Rucaparib inhibits PARP1, PARP2, PARP3 enzymes
- Directly binds PARP
- Inhibits enzymatic activity
- Prevents recruitment of repair proteins to site of damage
- Increases the formation of PARP-DNA complexes
- Prevents DNA repair and results in cell death

In tumor cell lines the inhibition of PARP in the presence of BRCA1/2 mutations led to increased rucaparib-induced cytotoxicity

Dosing

Initial: 600 mg (2x300 mg tablets) twice daily with or without food.
- Continue until disease progression or unacceptable toxicity

Dose modifications for adverse reactions:

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>600 mg twice daily (2x300 mg tablet)</td>
</tr>
<tr>
<td>First Dose Reduction</td>
<td>500 mg twice daily (2x250 mg tablet)</td>
</tr>
<tr>
<td>Second Dose Reduction</td>
<td>400 mg twice daily (2x200 mg tablet)</td>
</tr>
<tr>
<td>Third Dose Reduction</td>
<td>300 mg twice daily (1x300 mg tablet)</td>
</tr>
</tbody>
</table>
Contraindications and Adverse Reactions

No contraindications listed in manufacturer’s labeling

The most common:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>77%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>77%</td>
<td>5%</td>
</tr>
</tbody>
</table>

The more severe:

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Grade 1-4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>84%</td>
<td>25%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>77%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)

Precautions

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) and acute myeloid leukemia (AML)
- Rare reported cases of both in clinical trials
- Monitor blood counts at baseline and then monthly and as clinically indicated

Special Populations

Pregnant/Nursing
- No available data in pregnant women
- Based on animal studies and drug MOA, potential for fetal harm when administered to pregnant women
- Do not breast feed during treatment and 2 weeks after final dose
- Advise females of reproductive potential to use effective contraception during treatment and 6 months after

Drug-Drug Interactions

The effect of rucaparib on other drugs in humans has not been studied.

Place in therapy

For advanced ovarian cancer treatment of in patients with a deleterious BRCA mutation (germline and/or somatic) who have been treated with 2 or more chemotherapies
- Can be used in platinum-resistant or platinum-sensitive ovarian cancer
- Response rates were highest in patients who had a PFI ≥6 months or were limited to 2 prior lines of therapy

Price

<table>
<thead>
<tr>
<th>Dosage Strength</th>
<th>Wholesale Acquisition Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg #60</td>
<td>$6870.00</td>
</tr>
<tr>
<td>300 mg #60</td>
<td>$6870.00</td>
</tr>
</tbody>
</table>
Additional information

Granted accelerated approval by the FDA on 12/9/2016 based on response rates above 54% and duration of response of 9.2 months in total patient population in phase II trials.

- Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial.

Learning Assessment

Rucaparib is FDA approved for the treatment of advanced ovarian cancer with which mutation?

- A. p53
- B. BRCA 1/2
- C. BCR-ABL1
- D. BRAF V600

References


References (continued)


Learning Assessment
What is the route of administration of Spinraza and how often is the maintenance dose given?
A. Oral route, given only 1 time
B. Intrathecal route, given every 6 months
C. Intrathecal route, given every 4 months
D. SQ injection, given once a year

Speaker Disclosure
Syra Ruhl has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication
FDA approved indication:
◦ Treatment of spinal muscular atrophy (SMA)

Spinal Muscular Atrophy (SMA)
Neuromuscular disorder that typically presents in newborns (6 months-childhood)
Signs/Symptoms of SMA: hypotonia and muscle weakness
Genetic disorder which causes degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem
Characterized by progressive muscle weakness and atrophy

Drug Formulation
Spinraza is given intrathecally
Delivered into the lower back via a lumbar puncture and goes directly into the CNS
Procedure is done in a healthcare clinic/office
Sedation may be used depending on the condition of the patient
Allow solution to warm to room temperature
Administer within 4 hours of removal from vial
Before administering, remove 5 ml of CSF
Administer as a bolus
Mechanism of Action
Spinraza is an antisense oligonucleotide
Treats SMA caused by mutations in chromosome 5q leading to SMN (survival motor neuron) protein deficiency
SMN deficiency is one cause of SMA
Spinraza increases exon 7 inclusion in SMN2 mRNA transcripts and production of full length SMN protein

Pharmacokinetics
Absorption & Distribution – within the CNS and peripheral tissues (skeletal muscles, kidney, liver)
Metabolism - via exonuclease (3’ to 5’)-mediated hydrolysis
Excretion - in the urine

Dosing
Loading dose
- 12 mg once every 14 days for 3 doses; then 12 mg 1 time 30 days after the 3rd dose
Maintenance dose
- 12 mg every 4 months
Given intrathecally
Half life in CSF is 135-177 days, half life in plasma is 63-87 days

Special Populations
Pregnant – no adverse effects were seen in animal reproduction studies
Nursing – risk vs. benefit, it is not known if Spinraza is excreted in breast milk
Pediatric – dosing is same as adult
Geriatric – no experience in older patients, SMA is a disease of children and young adults
Hepatic Impairment – No dosage adjustments available in manufacturer’s labeling
Renal Impairment - No dosage adjustments available in manufacturer’s labeling

Contraindications
None

Contraindications & Precautions
Hematologic effects – Coagulation abnormalities and thrombocytopenia can occur, increased risk of bleeding complications
- Baseline & prior to each dose: platelet count and coagulation testing
Renal toxicity – including potentially fatal glomerulonephritis
- Baseline & prior to each dose: spot urine protein testing
Adverse Reactions
The most common: feeding difficulties/dysphagia, headache, constipation, back pain, respiratory tract infections
The more severe: scoliosis, proteinuria, hyponatremia, thrombocytopenia, renal toxicity

Drug-Drug Interactions
There are no known significant drug interactions

Price
Wholesale Acquisition Cost (WAC)
- $750,000 for first year
- $125,000 for 12mg/5mL vial

Place in therapy
Spinraza is the first and only drug approved for SMA
- Traditional therapy is supportive care
Treatment with Spinraza is recommended for most infants with SMA and for select children ages 2-12, decision to treat children and adults > 12 years old should be individualized

Additional information
There is limited published data of Spinraza in older children, adults, and patients with advanced disease.
Long term adverse effects with Spinraza are uncertain
Decision to treat should be individualized

Learning Assessment
What is the route of administration of Spinraza and how often is the maintenance dose given?
A. Oral route, given only 1 time
B. Intrathecal route, given every 6 months
C. Intrathecal route, given every 4 months
D. SQ injection, given once a year
References


Learning Assessment

What is an advantage to Trulance therapy over Linzess and Amitiza?

A. Trulance is less expensive than similar, alternative agents
B. Trulance is once daily dosing and can be given without regard to food
C. Trulance has less incidence of diarrhea than alternative agents
D. Trulance has an FDA approval for IBS-C

Speaker Disclosure

Austin Smith has no relevant financial relationships that would be considered a conflict of interest for the purposes of this program. This information will not include a discussion of non-FDA approved (off-label) medication use.

Indication

Chronic idiopathic constipation
Currently being evaluated for IBS-C

Chronic Idiopathic Constipation

Persistent constipation with no explanation
Affects approximately 14% of people
Affects more women and older adults
Includes symptoms of difficulty passing stools, hard stools, straining, or incomplete emptying lasting greater than 3 months

Mechanism of Action

GC-C (guanylate cyclase-C) agonist
Parent and active metabolite bind to GC-C and act locally on luminal surface of intestine
GC-C receptors are found on intestine surfaces are thought to play an important role in fluid and electrolyte regulation
Increased secretions of chloride and bicarbonate through cGMP leading to increased intestinal fluid and accelerated GI transit
Pharmacokinetics
Absorption – Negligibly absorbed systemically
Distribution – Minimally distributed to the tissues
Metabolism – Metabolism in GI tract to active ingredient then both parent and active form are proteolytically degraded in the intestinal lumen
Excretion – No excretion studies conducted, not measurable in plasma after administration

Dosing
3 mg tablet once daily
- With or without food
- Take with full glass of water

Special Populations
Boxed Warning: Do not use in children 5 years and younger due to risk of dehydration
Specific guidelines for renal or hepatic adjustments not available but adjustments likely not needed

Special Populations
Pregnancy: No adequate studies exist but animal studies suggest no effects on fetal development
Nursing: Small peptides may be absorbed and excreted into milk so providers must weigh risks and benefits of therapy
Geriatric: Use cautiously

Contraindications
Do not use in patients with known or suspected GI obstruction
Contraindicated in children 5 years and younger
Avoid in 6 to 18 year olds

Precautions
Do not administer to those with severe diarrhea
Notify physician if patients develop diarrhea
Use cautiously in patients at risk of mechanical GI obstruction
Avoid in 6 to 18 year olds
Adverse Reactions
The most common and severe adverse reaction is diarrhea. Others (<2%) include abdominal distention, flatulence, abdominal tenderness, elevated hepatic enzymes, and URTIs.

Drug-Drug Interactions
No known DDIs.

Price
Wholesale Acquisition Cost = $353.48 per bottle.

Place in therapy
No comparative trials exist with Trulance so it is difficult to say where in therapy it should be used. Studies against placebo show similar results to Linzess, another drug with the same MOA and Amitiza, an agent that increases fluid secretion through chloride channels. Should be used in the same place as Linzess as therapy for those who’ve failed other therapies or as primary therapy. Results and price similar between all three therapies but Amitiza is twice daily with food and Linzess must be taken 30 minutes before a meal.

Additional Information
Chronic idiopathic constipation can be hard to treat in specific individuals. Trulance may benefit patients who have not found relief through other agents. Counseling points:
- Swallow whole with a glass of water
- May crush and mix with apple sauce or mix with water
- Store in original container at room temperature.

Learning Assessment
What is an advantage to Trulance therapy over Linzess and Amitiza?
A. Trulance is less expensive than similar, alternative agents
B. Trulance is once daily dosing and can be given without regards to food
C. Trulance has less incidence of diarrhea than alternative agents
D. Trulance has an FDA approval for IBS-C
References


Suarw RC, Ford AC, Prevalence of and risk factors for chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011; 106(9) 1582.


Learning Assessment

As a monoclonal antibody, Zinplava (bezlotoxumab) targets:

- A. Transforming Growth Factor alpha (TGFα)
- B. Epidermal Growth Factor receptors (EGFRs)
- C. CD 20 on B cells
- D. Toxin A produced by C. difficile
- E. Toxin B produced by C. difficile
- F. Toxins produced by group A streptococcus

FDA approved Indication

Adjunctive therapy in pseudomembranous colitis caused by Clostridium difficile infection to reduce recurrence of Clostridium difficile infection in patients 18 years old and up who are receiving antibacterial drug treatment of C. difficile and are at a high risk for C. difficile recurrence.

FDA approved on Oct. 21, 2016

Pseudomembrane Colitis

Infectious diarrhea characterized by raised whitish, yellow plaques formed in the colon, caused by colonization of Clostridium Difficile resulting from antibiotic use, which releases toxin A and toxin B, causing colonic inflammation, diarrhea, and mucosa damage.

Drug Formulation

Preparation before use:

- Dilute in DSW or normal saline to final concentration of 1-10 mg/mL.

Administration:

- I.V. infusion over 60 min through a sterile, nonpyrogenic, low protein binding 0.2-5 micron in-line or add-on filter. No I.V. push or bolus. Infusion should be completed within 16 hours at room temperature or 24 hours for refrigerated preparation.
Mechanism of Action

Zinplava (bezlotoxumab) is a human IgG1 monoclonal antibody. It binds to C. difficile toxin B, neutralizes it and prevents its toxic effects. It does not bind to C. difficile toxin A.

C. Difficile overgrowth and colonization

Normal Colonic Flora

Toxin released

Toxin A, enterotoxin, causing diarrhea and inflammation

Toxin B, nonenterotoxin, damage colonic mucosa

Antibiotic use

Pharmacokinetics

Absorption: 100% (I.V. infusion.)
Distribution: Vd = 7.33L
Metabolized via protease catabolism
Excretion via protease catabolism. Half-Life ~ 19 days

Dosing

I.V. infusion
- 10 mg/kg as a single dose during antibacterial treatment for Clostridium difficile infection.
- Repeat doses have not been studied.

Special Populations

Pediatric: only approved for patients 18 years of age and older.
Hepatic Impairment: no adjustment needed.
Renal Impairment: no adjustment needed.
Pregnant: no animal studies performed. As a monoclonal antibody, Zinplava is expected to cross the placenta, with increasing amounts during the second and third trimesters.

Contraindications & Precautions

No absolute contraindications.
Precaution in heart failure patients: Zinplava increases risk of exacerbation of heart failure. Additionally, Zinplava use in patients with a history of heart failure increases mortality rate due to cardiac failure, infection, and respiratory failure. Therefore, in this population, Zinplava use should be reserved for situations when the benefits outweigh risks.

Adverse Reactions

The most common:
- Infusion related reaction (10%)
- Nausea (7%)
- Fever (5%)
- Headache (4%)

The more severe:
- Congestive heart failure (2.3%), primarily occurring in patients with underlying heart failure.
Drug-Drug Interactions
Belimumab: monoclonal antibodies may enhance the adverse/toxic effect of belimumab. Avoid combination.

Price
Wholesale Acquisition Cost
- 1000 mg/40 mL (40 mL): $3,800.00

Place in therapy
Adjunctive to antibacterial therapy
Secondary prevention of C. difficile infection in patients with high risk of recurrence.

Additional information
Zinplava is not an antibacterial drug and should not be used alone to treat C. difficile indication.

Learning Assessment
As a monoclonal antibody, Zinplava (bezlotoxumab) targets:
A. Transforming Growth Factor alpha (TGFα)
B. Epidermal Growth Factors (EGFs)
C. CD 20 on B cells
D. Toxin A produced by C. difficile
E. Toxin B produced by C. difficile
F. Toxins produced by group A streptococcus

References


