Disclosures

The presenter has reported no relevant financial relationships.
Learning Objectives

1. Evaluate treatment benefits and burdens of new drug approvals in nephrology practice.

2. Justify the use of new drug approvals in nephrology in your current practice.

3. Identify best practices for administering and monitoring new drug approvals in nephrology.

Outline

- Etelcalcetide (PARSABIV)
- Calcifediol (RAYALDEE)
- Ferric Pyrophosphate (TRIFERIC)
- Patiromer (VELTASSA)
- Ferric Citrate (AURYXIA)
Etelcalcetide (PARSABIV)

Brand Name
- Parsabiv (Amgen)
  - Approved February 2017

Pharmacologic Class
- Calcimimetic

Therapeutic Class
- Miscellaneous (AHFS – 92:92)

Available Dosage Form(s)
- Single use vials
  - 2.5 mg/0.5 mL
  - 5 mg/1 mL
  - 10 mg/2 mL

Etelcalcetide | Similar Drugs in Class

Cinacalcet (SENSIPAR)

Etelcalcetide | Indications & Dosage

Treatment of secondary HPT in adult patients with CKD on hemodialysis

- **Initial**: 5 mg IV bolus 3 times per week at the end of hemodialysis
- **Dosage adjustments**: Titrate dose in 2.5 mg or 5 mg increments not more frequently than every 4 weeks to a dose that maintains PTH levels within recommended target range and corrected serum calcium within the normal range; maximum maintenance dose: 15 mg three times per week; minimum maintenance dose: 2.5 mg three times per week
- **Conversion FROM cinacalcet**: Discontinue cinacalcet for at least 7 days prior to initiating etelcalcetide
- **Missed dose**: If hemodialysis is missed, do not administer. Resume etelcalcetide at the end of the next hemodialysis treatment. If doses are missed for >2 weeks, re-initiate with 5 mg (or 2.5 mg if that was the patient’s last dose) 3 times per week

Etelcalcetide | Dosage Adjustments

- Hepatic Impairment: NONE
- Geriatric: NONE
- Toxicity – Hypocalcemia
  - Stop therapy and treat hypocalcemia if the corrected serum calcium <7.5 mg/dL or hypocalcemia is symptomatic
  - When the corrected serum calcium is within normal limits, symptoms of hypocalcemia have resolved, and predisposing factors for hypocalcemia have been addressed, re-initiate at a dose 5 mg lower than the last administered dose
  - If the last administered dose was 2.5 mg or 5 mg, re-initiate at a dose of 2.5 mg


Etelcalcetide | Administration

**Administration**

Administer as an undiluted IV bolus into venous line of the dialysis circuit at the end of hemodialysis during or after rinse back. Do not mix or dilute prior to administration.

**Storage & Stability**

Store intact vials in refrigerator at 2°C to 8°C (36°F to 46°F) in original carton - protect from light. Once removed from refrigerator, use within 7 days (if stored in original carton) or within 4 hours (if removed from original carton).

Etelcalcetide | PK & PD

Mechanism of Action
Allosterically activates the calcium-sensing receptor (CaSR) on the parathyroid gland, resulting in decreased PTH secretion, and serum calcium and phosphorus levels.

Onset
PTH levels decrease within 30 minutes.

Time to Steady State
7 – 8 weeks (plasma).

Duration
Half-life = 3-4 days (hemodialysis).

Elimination
Metabolism = Undergoes biotransformation in blood to form conjugates with serum albumin
Excretion = Dialysate (~60% of administered dose; ~89% of recovered dose); urine (3.2%) and feces (4.5%)

Dialyzable
Yes

Etelcalcetide | Adverse Drug Events

- Greater than 10%:
  - Endocrine & metabolic: Decreased serum calcium (≤79%), hypophosphatemia (1% to 18%)
  - GI: Diarrhea (11%), nausea (11%)
  - Neuromuscular & skeletal: Muscle spasm (12%)
- 1% to 10%:
  - Cardiovascular: Prolonged Q-T interval on ECG (1% to 5%), cardiac failure (2%)
  - Central nervous system: Headache (8%), paresthesia (6%)
  - Endocrine & metabolic: Hypocalcemia (serum calcium < 7 m/dL: 8%), hyperkalemia (4%)
  - GI: Vomiting (9%)
  - Immunologic: Antibody development (7%; 80% of these patients have preexisting anti-etelcalcetide antibodies)
  - Neuromuscular & skeletal: Myalgia (2%)
# Etelcalcetide | Warnings & Precautions

## Interactions
Cinacalcet – may enhance the hypocalcemic effect of etelcalcetide

## Contraindications
Hypersensitivity to etelcalcetide or any component of the formulation.

## Pregnancy
Adverse events were observed in animal reproduction studies at doses which also caused maternal toxicity (including hypocalcemia)

## Lactation
It is not known if etelcalcetide is present in breast milk. Due to the potential for hypocalcemia in a breastfeeding infant, breastfeeding is not recommended by the manufacturer.

---


---

# Etelcalcetide | Medication Safety

## Monitoring
- Signs/symptoms of hypocalcemia, worsening of heart failure, GI bleeding/ulcerations; QT interval in patients at risk for QT interval prolongation and ventricular arrhythmia
- Corrected serum calcium levels: Prior to initiation and 1 week after dose initiation or adjustment; after the maintenance dose is established, monitor every 4 weeks
- PTH levels: Prior to initiation and 4 weeks after dose initiation or adjustment; after the maintenance dose is established, monitor per clinical practice

## Look – alike / Sound – alike
None

## REMS
None
Etelcalcetide | Patient Education

Medication Counseling

• Instruct patient to report symptoms of hypocalcemia

• Advise patient to report worsening heart failure

• Tell patient to report any symptoms of upper gastrointestinal bleeding

• Side effects may include muscle spasm, myalgia, diarrhea, nausea, vomiting, headache, or paresthesias


Etelcalcetide | Pivotal Trials

• Evaluated in two 26-week, randomized, double-blind, placebo-controlled clinical studies for the treatment of secondary HPT in adult patients with CKD on hemodialysis three times per week

• Patients were administered etelcalcetide at a starting dose of 5 mg three times per week at the end of hemodialysis; the dose was titrated every 4 weeks until week 17 to a maximum of 15 mg three times per week to achieve a target PTH level ≤300 pg/mL

• Patients in both treatment arms could be treated with vitamin D sterols and/or phosphate binders

• Etelcalcetide was suspended temporarily if two consecutive PTH levels were less than 100 pg/mL
  – The dose of etelcalcetide was not increased if PTH levels were less than or equal to 300 pg/mL, corrected serum calcium was less than 8.3 mg/dL, symptomatic hypocalcemia occurred, or the investigator judged that no dose increase was needed

• Mean baseline PTH levels were 834.2 pg/mL and 848.4 pg/mL, respectively

Etelcalcetide | Pivotal Trials (continued)

- The primary end point for both studies was the proportion of patients who achieved a > 30% reduction from baseline in mean PTH during the efficacy assessment phase (EAP; weeks 20 through 27, inclusive)
  - The secondary endpoints were the proportion of patients with a mean PTH of less than or equal to 300 pg/mL, percent change from baseline in PTH, corrected serum calcium, and phosphate levels
- In both studies, a significantly higher proportion of patients treated with etelcalcetide achieved a greater than 30% reduction in mean PTH levels from baseline to the EAP than the proportion of patients treated with placebo
- The common adverse reactions reported in the combined placebo-controlled studies in etelcalcetide - treated patients compared to placebo were decreased blood calcium (64% vs 10%), muscle spasms (12% vs 7%), diarrhea (11% vs 9%), nausea (11% vs 6%), vomiting (9% vs 5%), headache (8% vs 6%), hypocalcemia (7% vs 0.2%), and paresthesia (6% vs 1%). Overall, 1% of etelcalcetide-treated patients and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.


Calcifediol (RAYALDEE)
### Calcifediol

<table>
<thead>
<tr>
<th><strong>Brand Name</strong></th>
<th>Rayaldee (OPKO Pharmaceuticals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approved June 2016</td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacologic Class**  
Vitamin D analogue

**Therapeutic Class**  
Vitamin D (AHFS – 88:16)

**Available Dosage Form(s)**  
30 mcg capsule, extended release

---

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.

---

### Calcifediol | Similar Drugs in Class

- **Doxercalciferol**
- **Paracalcitrol**
- **Calcitriol**

---

Calcifediol | Indications & Dosage

Treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL

- 30 mcg once daily at bedtime; may increase to 60 mcg once daily at bedtime after 3 months if intact PTH remains above desired therapeutic range
- **Note:** Ensure corrected serum total calcium is below 9.8 mg/dL prior to initiating therapy.
- Maintenance dose should target total 25-hydroxyvitamin D levels between 30 and 100 ng/mL, intact PTH levels within desired therapeutic range, serum calcium <9.8 mg/dL, and serum phosphorus ≤5.5 mg/dL

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.

Calcifediol | Dosage Adjustments

- Hepatic Impairment: NONE
- Geriatric: NONE
- Toxicity – Hypercalcemia, low PTH, or serum total 25-hydroxyvitamin D > 100 ng/mL
  - Temporarily discontinue therapy for persistently low intact PTH levels, or consistently elevated calcium or 25-hydroxyvitamin D levels (> 100 ng/mL)
  - Resume therapy at a reduced dose after laboratory values have normalized

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.
Calcifediol | Administration

**Administration**
- Administer at bedtime
- Swallow capsule whole

**Storage & Stability**
- Store at 20°C to 25°C (68°F to 77°F)
- Excursions permitted to 15°C to 30°C (59°F to 86°F)

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.

Calcifediol | PK & PD

**Mechanism of Action**
- A prohormone of the active form of vitamin D₃, calcitriol (1,25 dihydroxyvitamin D₃), is catalyzed to calcitriol by the 1-alpha-hydroxylase enzyme
- Calcitriol binds to vitamin D receptors in target tissues activating vitamin D responsive pathways resulting in increased intestinal absorption of calcium and phosphorus and reduced parathyroid hormone synthesis

**Onset**
- ~ 2 weeks (maximum effect ~ 3 months)

**Distribution**
- > 98% protein bound

**Duration**
- Half-life = ~ 25 days (CKD: Stage 3 and 4)

**Elimination**
- **Metabolism** = primarily to calcitriol by CYP27B1 (1-alpha-hydroxylase enzyme) in the kidney
- **Excretion** = Feces

**Dialyzable**
- No
**Calcifediol | Adverse Drug Events**

- **Greater than 10%:**
  - Hematologic & oncologic: Abnormal phosphorus levels (increased: 45%; hyperphosphatemia: <1%)

- **1% to 10%:**
  - Cardiovascular: Congestive heart failure (4%)
  - Endocrine & metabolic: Hypercalcemia (4%; patients requiring dose reduction for hypercalcemia: 2%), hyperkalemia (3%), hyperuricemia (2%)
  - Hematologic & oncologic: Anemia (5%), bruise (2%)
  - Neuromuscular & skeletal: Osteoarthritis (2%)
  - Renal: Increased serum creatinine (5%)
  - Respiratory: Nasopharyngitis (5%), cough (4%), dyspnea (4%), bronchitis (3%), chronic obstructive pulmonary disease (1%), pneumonia (1%)

**Calcifediol | Drug Interactions**

- **Aluminum Hydroxide** - *Avoid combination*
- **Bile Acid Sequestrants** - *Consider therapy modification*
- **Calcium Salts** - *Monitor therapy*
- **Cardiac Glycosides** - *Monitor therapy*
- **CYP3A4 Inducers (Strong)** - *Monitor therapy*
- **CYP3A4 Inhibitors (Strong)** - *Monitor therapy*
- **Danazol** - *Monitor therapy*
- **Mineral Oil** - *Consider therapy modification*
- **Multivitamins/Fluoride (with vitamins ADE)** - *Avoid combination*
- **Multivitamins/Minerals (with ADEK, Folate, Iron)** - *Avoid combination*
- **Orlistat** - *Consider therapy modification*
- **Sucralfate** - *Avoid combination*
- **Thiazide Diuretics** - *Monitor therapy*
- **Vitamin D Analogs** - *Avoid combination*
**Calcifediol | Warnings & Precautions**

**Contraindications**

Hypersensitivity to calcifediol or any component of the formulation

**Pregnancy**

- Category C
- Adverse events were observed in animal reproduction studies. Endogenous calcifediol crosses the placenta in concentrations generally lower than those in the maternal plasma; supplementation increases cord blood 25OHD concentrations.

**Lactation**

- Endogenous calcifediol is poorly excreted into breast milk, but milk concentrations may be increased with supplementation
- The manufacturer recommends that caution be used if administered to a nursing woman

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.

---

**Calcifediol | Medication Safety**

**Monitoring**

- Serum calcium, serum phosphorus, serum total 25-hydroxyvitamin D and intact PTH levels within 3 months after initiation of therapy or dose adjustment and, subsequently at least every 6 to 12 months
- Signs and symptoms of hypercalcemia

**Look – alike / Sound – alike**

None

**REMS**

None

**Safety pearl**

DO NOT crush or open

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.
Calcifediol | Patient Education

Medication Counseling

• Instruct patient to report symptoms of hypercalcemia

• Side effects may include anemia, nasopharyngitis, dyspnea, congestive heart failure, and constipation

• Advise patient to take capsule at bedtime

• Counsel patient to skip a missed dose and resume normal dosing schedule

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.

Calcifediol | Pivotal Trials

• The efficacy and safety of calcifediol were evaluated in two identical multicenter, randomized, placebo-controlled, double-blind trials in patients with secondary hyperparathyroidism, stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels between 10 and 30 ng/mL

• Subjects were stratified by chronic kidney disease stage and randomized in a 2:1 ratio to receive calcifediol or a matching placebo at bedtime over 26 weeks

• The dose of calcifediol was 30 mcg once daily for the first 12 weeks and either 30 or 60 mcg once daily for the last 14 weeks
  – The dose was increased to 60 mcg at the start of week 13 if the plasma intact PTH level was greater than 70 pg/mL, the serum 25-hydroxyvitamin D level was less than 65 ng/mL and the serum calcium level was less than 9.8 mg/dL

• A total of 213 subjects were randomized in one trial (72 received placebo and 141 received calcifediol), and 216 subjects were randomized in the second trial (72 received placebo and 144 received calcifediol)

• The subjects’ mean age was 66 years (range 25-85), 50% were male, 65% White, 32% African-American or Black and 3% Other

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.
Calcifediol | Pivotal Trials (continued)

- At baseline, subjects had secondary hyperparathyroidism, and stage 3 (52%) or stage 4 (48%) chronic kidney disease without macroalbuminuria.
- Tmean baseline intact PTH was 130 pg/mL for subjects with stage 3 disease (n = 222) and 166 pg/mL for subjects with stage 4 disease (n = 207).
- Mean serum calcium was 9.2 mg/dL, mean serum phosphorus was 3.7 mg/dL and mean serum 25-hydroxyvitamin D was 20 ng/mL.
  - Of the 429 subjects randomized, 354 (83%) completed the studies.
- The primary analysis compared the proportion of individuals who experienced an at least 30% reduction in plasma intact PTH from baseline to end of trial (average of weeks 20, 22, 24 and 26).
  - A larger proportion of patients randomized to calcifediol experienced an at least 30% reduction in plasma intact PTH from baseline compared to placebo in both trials (33% versus 8% in the first trial (P < 0.001).
- Serum total 25-hydroxyvitamin D levels increased to at least 30 ng/mL in 80% and 83% of subjects treated with calcifediol vs. 3% and 7% of subjects treated with placebo (P < 0.001) in the two studies, respectively.

1. Rayaldee (calcifediol) [prescribing information]. Miami, FL: Opko Pharmaceuticals, LLC; July 2016.
Ferric pyrophosphate

Brand Name  
Triferic (Rockwell Medical, Inc.)  
• Approved January 2015

Pharmacologic Class  
Iron salt

Therapeutic Class  
Iron preparations (AHFS – 20:04.04)

Available Dosage Form(s)  
• 272 mg packet  
• 27.2 mg / 5 mL solution for injection

1. Triferic (ferric pyrophosphate citrate) [prescribing information].  
Wixom, MI: Rockwell Medical Inc.; January 2015.

Ferric pyrophosphate | Similar Drugs in Class

- Ferric Carboxymaltose
- Ferumoxytol
- Iron Sucrose
- Sodium Ferric Gluconate Complex
- Iron Dextran

Ferric pyrophosphate | Indications & Dosage

Replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease

- Intradialytic: after admixture into bicarbonate concentrate dialysate (final concentration 2 micromolar [110 mcg/L]) use at each dialysis session
- Therapy may be continued for as long as the patient is receiving maintenance hemodialysis for CKD
- **NOTE**: ampules contain 5.44 mg elemental iron per mL; powder packet contains 272 mg elemental iron per packet
- **No dosage adjustment necessary for renal or hepatic impairment**

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.

Ferric pyrophosphate | Administration

**Administration**

- Intradialytic - administer after admixed into bicarbonate concentrate dialysate at each dialysis session

**Dose Preparation**

- Solution in ampules may appear slightly yellow-green in color. Add solution or powder to bicarbonate concentrate used for generation of hemodialysate (2 micromolar [110 mcg/L] iron final concentration)
- Multiple 5 mL ampules can be added to the master bicarbonate mix at a ratio of one 5 mL ampule to each 9.46 L (2.5 gal) of bicarbonate concentrate
- Multiple powder packets can be added to the master bicarbonate mix at a ratio of one powder packet to each 94.6 L (25 gal) of bicarbonate concentrate

**Storage & Stability**

- Store at 20°C to 25°C (68°F to 77°F)
- Use hemodialysate within 24 hours of preparation
- Protect ampules from light

Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.
Ferric pyrophosphate | PK & PD

**Mechanism of Action**
- Iron in the form of ferric pyrophosphate citrate and added to hemodialysate solution is administered to patients by transfer across the dialyzer membrane
- Iron delivered into the circulation binds to transferrin for transport to erythroid precursor cells to be incorporated into hemoglobin

**Absorption**
33% reduction in amount of iron delivered with decreased blood and dialysate flow rates

**Distribution**
Vd: 0.765 to 2.08 L

**Duration**
Half-life = ~ 1.5 hours

**Elimination**
Total body clearance: 0.406 to 0.672 L/hr

**Dialyzable**
Unlikely

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.

---

Ferric pyrophosphate | Adverse Drug Events

- Greater than 10%:
  - Cardiovascular: Procedural hypotension (22%)
- 1% to 10%:
  - Cardiovascular: Peripheral edema (7%), clotted AV fistula (3%), dialysis access hemorrhage (3%)
  - Central nervous system: Headache (9%), fatigue (4%), dizziness
  - Dermatologic: Pruritus
  - Gastrointestinal: Constipation, nausea
  - Genitourinary: Urinary tract infection (5%)
  - Neuromuscular & skeletal: Muscle spasm (10%), limb pain (7%), back pain (5%), weakness (4%)
  - Respiratory: Dyspnea (6%)
  - Miscellaneous: Fever (5%)

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.
### Ferric pyrophosphate | Warnings & Precautions

**Interactions**
- Dimercaprol - *Avoid combination*
- Entacapone - *Consider therapy modification*

**Contraindications**
Hypersensitivity to ferric pyrophosphate or any component of the formulation

**Pregnancy**
Adverse events were observed in animal reproduction studies. Females of reproductive potential should use effective contraception during treatment and for at least 2 weeks following completion of therapy.

**Lactation**
It is not known if iron from this preparation is excreted in breast milk. According to the manufacturer, the decision to breast-feed during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother.

---

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.

### Ferric pyrophosphate | Medication Safety

**Monitoring**
- Monitor for hypersensitivity reactions during and after the dialysis session
- Determine iron status on pre-dialysis blood samples, as post-dialysis serum iron parameters may overestimate serum iron and transferrin saturation
- Patients with CKD should have anemia indices (including hemoglobin, hematocrit, and iron studies) assessed as clinically indicated in routine care

**Look – alike / Sound – alike**
None

**REMS**
None

---

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.
Ferric pyrophosphate | Patient Education

Medication Counseling

• Recommend female patient avoid pregnancy during treatment and for at least 2 weeks after discontinuation

• Side effects may include peripheral edema, arteriovenous fistula thrombosis or hemorrhage, pyrexia, fatigue, asthenia, urinary tract infection, muscle spasm, extremity pain, back pain, or dyspnea

• Instruct patient to report symptoms of hypersensitivity

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.

Ferric pyrophosphate | Pivotal Trials

• The safety and efficacy of ferric pyrophosphate in patients with HDD-CKD was assessed in two randomized, single blind, placebo-controlled trials

• Patients with hemoglobin of 9 g/dL to 12 g/dL with TSAT > 20% and serum ferritin concentrations > 200 mcg/L were included

• Patients were to remain in randomized treatment until pre-specified hemoglobin or ferritin criteria were met, indicating the need for a change in anemia management or if they completed 48 weeks

• Ferric pyrophosphate was added to bicarbonate concentrate with a final concentration of 110 mcg iron/L in the dialysate and was administered 3 or 4 times per week during hemodialysis

• Most patients were receiving stable dose of erythropoiesis stimulating agents (ESAs) at baseline

  – After randomization, patients’ ESA doses were not to be changed

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.
Ferric pyrophosphate | Pivotal Trials (continued)

- In Study 1, the mean age of patients was 58 years (range 23 to 89); 32% were female, 55% were Caucasian, 32% were African American, and 13% were other races.
- In Study 2, the mean age of patients was 58 years (range 20 to 89); 41% were female, 54% were Caucasian, 40% were African American, and 6% were other races.
- The primary endpoint of the studies was the mean change in hemoglobin from baseline to the end-of-treatment period (mean hemoglobin of the last one-sixth (1/6th) of the time in the randomized treatment period).
- About 18% of patients completed the planned 48-week treatment duration.

1. Triferic (ferric pyrophosphate citrate) [prescribing information]. Wixom, MI: Rockwell Medical Inc.; January 2015.

Patiromer (VELTASSA)
## Patiromer

| Brand Name | Veltassa (OPKO Pharmaceuticals)  
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Approved October 2015</td>
</tr>
<tr>
<td>Pharmacologic Class</td>
<td>Potassium Binder</td>
</tr>
</tbody>
</table>
| Therapeutic Class | Potassium-removing agent  
|  | (AHFS – 40:18.18) |
| Available Dosage Form(s) | Powder packet  
|  | • 8.4 gm, 16.8 gm, 25.2 gm |


## Patiromer | Similar Drugs in Class

### Sodium Polystyrene Sulfonate (SPS)

Patiromer | Indications & Dosage

Treatment of hyperkalemia

- **Initial:** 8.4 g once daily
- Adjust dose at ≥ 1-week intervals in increments of 8.4 g
- **Maximum dose:** 25.2 g/day
- **No dosage adjustment necessary for geriatric patients or renal and hepatic impairment**


Patiromer | Administration

**Administration**
- Administer with food
- Do not administer patiromer in its dry form
- Following reconstitution, drink mixture immediately
- If powder remains in the glass after drinking, add more water, stir, and drink immediately
- Do not heat patiromer (e.g., microwave) or add to heated foods or liquids
- Administer other oral meds at least 3 hours before or 3 hours after patiromer and monitor for clinical response and/or blood levels where possible

**Storage & Stability**
- Store at 2 °C to 8 °C (36 °F to 46 °F)
- If stored at room temperature (25 °C ± 2 °C [77 °F ± 4 °F]), use within 3 months of being taken out of the refrigerator
- Avoid exposure to excessive heat above 40 °C (104 °F)

Patiromer | PK & PD

Mechanism of Action
A non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, increases fecal potassium excretion through binding of potassium in the lumen of the gastrointestinal tract, resulting in a reduction of serum potassium levels.

Onset
7 hours (peak response in ~ 48 hours)

Distribution
Not systemically absorbed

Duration
~ 24 hours

Elimination
Metabolism = None
Excretion = Feces

Dialyzable
No


---

Patiromer | Adverse Drug Events

- **1% to 10%:**
  - Endocrine & metabolic: Hypomagnesemia (5% to 9%), hypokalemia (5%)
  - Gastrointestinal: Constipation (7%; transient), diarrhea (5%), abdominal distress (2%), flatulence (2%), nausea (2%)

Patiromer | Warnings & Precautions

Interactions
Consider therapy modification
- Ciprofloxacin
- Levothyroxine
- Metformin

Contraindications
Hypersensitivity to patiromer or any component of the formulation

Pregnancy
Not absorbed systemically following oral administration. Use during pregnancy is not expected to result in significant exposure to the fetus.

Lactation
Not absorbed systemically following oral administration. Breast-feeding is not expected to result in significant exposure to a nursing child


Patiromer | Medication Safety

Monitoring
- Obtain serum potassium and serum magnesium
- Instruct patient to take other medications at least three hours before or three hours after patiromer

Look – alike / Sound – alike
None

REMS
None

Patiromer | Pivotal Trials

• In Part A, 243 patients were treated with patiromer for 4 weeks
• Patients with a baseline serum potassium of 5.1 mEq/L to < 5.5 mEq/L received a starting patiromer dose of 8.4 grams patiromer per day (as a divided dose) and patients with a baseline serum potassium of 5.5 mEq/L to < 6.5 mEq/L received a starting patiromer dose of 16.8 grams patiromer per day (as a divided dose)
• The dose of patiromer was titrated based on the serum potassium level, assessed starting on Day 3 and then at weekly visits (Weeks 1, 2 and 3) to the end of the 4-week treatment period, with the aim of maintaining serum potassium in the target range (3.8 mEq/L to < 5.1 mEq/L)
• The mean age of patients was 64 years, 58% of patients were men, and 98% were Caucasian; approximately 97% of patients had hypertension, 57% had type 2 diabetes, and 42% had heart failure
• Part A secondary endpoint: 76% (95% confidence interval: 70%, 81%) of patients had a serum K+ in the target range of 3.8 mEq/L to < 5.1 mEq/L at Week 4
• The mean daily doses of patiromer were 13 grams and 21 grams in patients with serum K+ of 5.1 to < 5.5 mEq/L and 5.5 to < 6.5 mEq/L, respectively

Patiromer | Pivotal Trials (continued)

• In Part B, 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to < 6.5 mEq/L and whose serum potassium was in the target range (3.8 mEq/L to < 5.1 mEq/L) at Part A Week 4 and still receiving RAAS inhibitor medication were randomized to continue patiromer or to receive placebo to evaluate the effect of withdrawing patiromer on serum potassium
  – In patients randomized to the patiromer group, the mean daily dose was 21 grams at the start of and during Part B
• The Part B primary endpoint was the change in serum K+ from Part B baseline to the earliest visit at which the patient’s serum potassium was first outside of the range of 3.8 to < 5.5 mEq/L, or to Part B Week 4 if the patient’s serum K+ remained in the range
• In Part B, serum potassium rose by 0.72 mEq/L in patients who were switched to placebo, versus no change in patients who remained on patiromer
• More placebo patients (91%; 95% CI: 83%, 99%) developed a serum K+ ≥ 5.1 mEq/L at any time during Part B than patiromer patients (43%; 95% CI: 30%, 56%), p < 0.001
• More placebo patients (60%; 95% CI: 47%, 74%) developed a serum L+ ≥ 5.5 mEq/L at any time during Part B than patiromer patients (15%; 95% CI: 6%, 24%), p < 0.001

Ferric Citrate
(AURYXIA)

Brand Name
• Auryxia (Keryx Biopharmaceuticals)
  • Approved September 2014

Pharmacologic Class
Phosphate Binder

Therapeutic Class
Phosphate-removing agent
(AHFS – 40:18.19)

Available Dosage Form(s)
210 mg tablet

Ferric citrate | Similar Drugs in Class

Calcium Carbonate  Calcium Acetate  Sevelamer

Lanthanum Carbonate  Sucroferric Oxyhydroxide


Ferric citrate | Indications & Dosage

For the control of serum phosphorus levels in patients with chronic kidney disease (CKD) receiving dialysis

1. Initial: 2 tablets (420 mg ferric iron) 3 times daily

2. Maintenance: Increase or decrease dose by 1 tablet or 2 tablets (210 mg to 420 mg ferric iron) as needed at 1 week or longer intervals to achieve target serum phosphorus levels

3. Maximum dose: 12 tablets [2,520 mg ferric iron] daily

4. No dosage adjustment necessary for geriatric patients or renal and hepatic impairment


**Ferric citrate | Administration**

**Administration**
- Administer with meals
- Ensure adherence with prescribed diet

**Storage & Stability**
- Store at 20°C to 25°C (68°F to 77°F)
- Excursions are permitted between 15°C and 30°C (59°F and 86°F)
- Protect from moisture.


**Ferric citrate | PK & PD**

**Mechanism of Action**
- Lowers serum phosphate by binding to dietary phosphate in the GI tract
- Product precipitates as insoluble ferric phosphate and is excreted in feces

**Distribution**
- Systemically absorbed

**Elimination**
- Metabolism = None
- Excretion = Feces

**Dialyzable**
- Unknown

Ferric citrate | Adverse Drug Events

- Gastrointestinal: Diarrhea (21%), nausea (11%), constipation (8%), vomiting (7%), darkening of stools

- Respiratory: Cough (6%)


Ferric citrate | Drug Interactions

- Alpha-Lipoic Acid - Consider therapy modification
- Bisphosphonate Derivatives - Consider therapy modification
- Cefdinir - Consider therapy modification
- Deferiprone - Consider therapy modification
- Dimercaprol - Avoid combination
- Dolutegravir - Consider therapy modification
- Eltrombopag - Consider therapy modification
- Entacapone - Consider therapy modification
- Ferric Hydroxide Polymaltose Complex - Consider therapy modification
- Levodopa - Consider therapy modification
- Levothyroxine - Consider therapy modification
- Methyldopa - Consider therapy modification
- Penicillamine - Consider therapy modification
- Phosphate Supplements - Consider therapy modification
- Quinolone Antibiotics - Consider therapy modification
- Tetracyclines - Consider therapy modification
- Trientine - Consider therapy modification
## Ferric citrate | Warnings & Precautions

### Contraindications
- Hypersensitivity to ferric citrate or any component of the formulation
- Iron overload syndromes (e.g., hemochromatosis)

### Pregnancy
- Category B
- Animal reproduction studies have not been conducted. Use of ferric citrate may increase iron stores, which may cause adverse events in pregnancy (fetal malformations, spontaneous abortion, and gestational diabetes noted with iron overdose in pregnant women).

### Lactation
- It is not known if ferric citrate is excreted into breast milk
- The manufacturer notes that exposure to a nursing infant is possible

---

### Ferric citrate | Medication Safety

#### Monitoring
- Evaluate serum iron, ferritin, and transferrin saturation (TSAT) at baseline and during therapy
- Periodically monitor serum phosphorus to assess therapy and adjust dosage if necessary

#### Look – alike / Sound – alike
- None

#### REMS
- None

---

Ferric citrate | Pivotal Trials

• The ability of ferric citrate to lower serum phosphorus in patients with CKD on dialysis was demonstrated in randomized clinical trials: one 56-week, safety and efficacy trial, consisting of a 52-week active-controlled phase and a 4-week, placebo-controlled, randomized withdrawal period, and one 4-week open-label trial of different fixed doses of ferric citrate. Both trials excluded subjects who had an absolute requirement for aluminum containing drugs with meals.

• **Long-term, Randomized, Controlled, Safety and Efficacy Trial**
  – After the 2-week washout period during which phosphate binders were held, patients with a mean serum phosphorus of 7.5 mg/dL during washout were randomized 2:1 to ferric citrate (N=292) or active control (calcium acetate and/or sevelamer carbonate; N=149). The majority (>96%) of subjects were on hemodialysis.
  – The starting dose of ferric citrate was 6 tablets/day, divided with meals. The starting dose of active control was the patient’s dose prior to the washout period. The dose of phosphate binder was increased or decreased as needed to maintain serum phosphorus levels between 3.5 and 5.5 mg/dL, to a maximum of 12 tablets/day.
  – Serum phosphorus levels declined following initiation of therapy. The phosphorus lowering effect was maintained over 52 weeks of treatment.


Ferric citrate | Pivotal Trials (continued)

• **Fixed-Dose Trial**
  – Following a 1- to 2-week washout from all phosphate-binding agents, 154 patients with hyperphosphatemia (mean serum phosphorus of 7.5 mg/dL) and CKD on dialysis were randomized in a 1:1:1 ratio to 1, 6, or 8 tablets/day of ferric citrate for 4 weeks.
  – Ferric Citrate was administered with meals; subjects receiving 1 tablet/day were instructed to take it with their largest meal of the day, and subjects on 6 or 8 tablets/day took divided doses in any distribution with meals.
  – Dose-dependent decreases in serum phosphorus were observed by Day 7 and remained relatively stable for the duration of treatment.
  – Demonstrated reduction from baseline to Week 4 in mean serum phosphorus were significantly greater with 6 & 8 tabs/day than with 1 tabs/day (p < 0.0001).
  – Mean reduction in serum phosphorus at Week 4 was 0.1 mg/dL with 1 tablet/day, 1.9 mg/dL with 6 tablets/day, and 2.1 mg/dL with 8 tablets/day.

What’s in the Pipeline?

• **Amgen**
  – www.amgenpipeline.com

• **Shire**

• **Otsuka**

• **Roche**
  – http://www.roche.com/research_and_development/who_we_are/how_we_work/pipeline.htm

• **Advicenne**

Key Takeaways

• Takeaway #1
  – New drug approvals in nephrology are targeting long-standing CKD-related comorbidities that have proved stubborn to manage: bone/mineral disease and iron deficiency/anemia

• Takeaway #2
  – Data is still lacking in regards to the quality outcomes and comparative efficacy related to new drug approvals in nephrology

• Takeaway #3
  – Drugs don’t work in patients who don’t take them. Regular communication with patient and providers on adherence, appropriate administration, and adverse effects/drug interactions is key to positive patient outcomes.
Additional Resources

• Drug Information Portal (NIH)
  – Quick access to quality drug information

• GlobalRPh
  – www.globalrph.com
  – The clinician’s ultimate reference

• Institute for Safe Medication Practices (ISMP)
  – http://www.ismp.org/
  – Educating the healthcare community and consumers about safe medication practices

Question and Answer Session