DISCLOSURES

- Heather, Brittney and Steve work for Rocky Mountain Health Plans.
- We do not have any financial interest in the medications we are discussing today.
- We have no intention to malign any person, business or product.
Pre-Test

Turn on your iClickers!
QUESTION 1

Which drug is indicated for asthma and COPD?

A. Stiolto Respimat
B. Seebri Neohaler
C. Spiriva HandiHaler
D. Spiriva Respimat
In terms of efficacy, there is a clinical difference between the 3 drugs in the LAMA/LABA class (Utibron Neohaler, Anoro Ellipta, and Stiolto Respimat).

A. True  
B. False
QUESTION 3

Which of the following medications are FDA approved to treat chronic pain?

A. Bunavail
B. Zubsolv
C. Belbuca
D. Suboxone
INHALERS FOR COPD
SEEبري AND UTIBRON NEOHALER

adjective | me – too in·hal·er | \ˈmē-ˈtŭ in-ˈhā-lər\

Full Definition
: a device that allows you to breathe the same no matter what brand you choose
NEW COPD INHALER
SEEبري NEOHALER (GLYCOPYRROLATE)

- **Class:** LAMA (long-acting anticholinergic)

- **Indication:** Maintenance treatment of airflow obstruction in patients with COPD

- **Dosing:** Inhale contents of 1 capsule BID

- **DIs:** Similar to other LAMAs
  - Additive anticholinergic effects if given with other anti-cholinergic medications
NEW COPD INHALER
SEEBRI NEOHALER (GLYCOPYRROLATE)

**SE:** Similar to other LAMAs
- URTI (< 2%)
- Nasopharyngitis (2%)

**W/P:** Similar to other LAMAs
- Worsening of narrow-angle glaucoma, urinary retention, and paradoxical bronchospasm
- Pregnancy category C
New COPD Inhaler
Seebri Neohaler (Glycopyrrolate)

- Clinical Studies – Trial 1 and 2 (n = 867)
  - 12-week, R, DB, parallel-group trials in COPD patients
  - Seebri vs placebo
  - Primary endpoint: Change from baseline in FEV1
    - Significant increase with Seebri vs placebo
    - Treatment difference: 139 mLs (Trial 1) and 123 mLs (Trial 2)
NEW COPD INHALER
SEEبري NEOHALER (GLYCOPRRELATE)

Secondary endpoints

- # of rescue albuterol doses decreased with Seebri vs placebo

- QOL improved clinically in trial 2, but not in trial 1
  - QOL was based on SGRQ
  - MCID is an improvement in score of ≥ 4 points
  - **Trial 1:** 49% of Seebri patients improved their score by ≥ 4 points vs 41% for placebo [OR: 1.43, 95% CI: 0.95, 2.15]
  - **Trial 2:** 55% vs 42% [OR: 1.78; 95% CI: 1.17, 2.71]
# Class Comparison - LAMAs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Use</th>
<th>Dose</th>
<th>Device</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Incruse Ellipta**     | COPD                       | 1 puff daily | DPI    | **Cost:** similar  
  • Incruse slightly less ($300 vs $350)                                  |
| **Spiriva HandiHaler**  | COPD + COPD exacerbation  | 1 cap daily | DPI    | **Dose**  
  • Incruse is the only “1 puff daily” inhaler  
  • Others use capsules (require multiple puffs) or are BID               |
| **Spiriva Respimat**    | COPD + Asthma + COPD       | 2 puffs daily | Respimat-Soft Mist | **Efficacy:** similar                                                   |
| **Tudorza Pressair**    | COPD                       | 1 puff BID  | DPI    | **SE:** similar                                                          |
| **Seebri Neohaler**     | COPD                       | 1 cap BID   | DPI    | **W/P:** Spiriva has additional warning for close monitoring of patients with mod - sev renal impairment (CrCl <60 mL/min)  
  • **Spiriva Respimat:** only LAMA indicated for asthma                |

**(umeclidinium)**  
**(tiotropium)**  
**(aclidinium)**  
**(glycopyrrolate)**
New COPD Inhaler
Utibron (Glycopyrrolate/Indacaterol)

- Class: LAMA/LABA

- Indication: Maintenance treatment of airflow obstruction in patients with COPD

- Dosing: 1 inhalation BID

- SE: Similar to other LAMA/LABAs
  - Nasopharyngitis (4%)
  - HTN (2%)
NEW COPD INHALER
UTIBRON (GLYCOPYRROLATE/INDACATEROL )

- **DI s:** Similar to other LAMA/LABAs

- **W/P:** Similar to other LAMA/LABAs
  - Worsening of narrow-angle glaucoma, urinary retention, and paradoxical bronchospasm
  - Indacaterol –CV effects; hypo or hyperkalemia
  - No adequate and well-controlled studies in pregnant women
Clinical Studies – Trial 1 and 2 (n = 2087)

- 12-week, R, DB, parallel-group trials in COPD patients
- Utibron vs placebo and vs individual components
- Primary endpoint: Change from baseline in FEV1
  - Significant increase with Utibron vs placebo and individual components
  - Treatment difference from placebo, indacaterol and glycopyrrolate:
    - Trial 1: 262 mLs, 112 mLs, 79 mLs
    - Trial 2: 231 mLs, 94 mLs, 98 mLs
Secondary endpoints
- # of rescue albuterol doses decreased with Utibron
- QOL improved clinically in trial 2
  - 57% of Utibron patients improved their score by ≥ 4 points vs ~50% for both glycopyrrolate and indacaterol and 39% for placebo
  - OR 1.6 (95% CI 1.1, 2.3) for Utibron v glycopyrrolate
  - OR 1.5 (95% CI 1.1, 2.2) for Utibron v indacaterol
  - OR 2.2 (95% CI 1.51, 3.2) for Utibron v placebo
- Trial 1 ORs showed significance for Utibron v placebo only
NEW COPD INHALER
UTIBRON (GLYCOPYRRROLATE/INDACATEROL )

- Clinical Studies – Trial 3
  - 52-week, long-term safety trial
  - R, DB, ACT that showed a significant increase of 80 mLs in FEV1 compared to indacaterol 75 mcg once-daily
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Use</th>
<th>Dose</th>
<th>Device</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Utibron Neohaler</strong></td>
<td>COPD</td>
<td>1 cap BID</td>
<td>DPI</td>
<td>• <strong>Cost</strong>: similar</td>
</tr>
<tr>
<td><em>(glycopyrrolate/indacaterol)</em></td>
<td></td>
<td></td>
<td></td>
<td>• <strong>Dose</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▪ Anoro has most friendly dosing at 1 puff daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• <strong>Efficacy</strong>: similar</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>• <strong>SE</strong>: similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Data for all LAMA/LABAs do not support a labeling claim for the reduction of exacerbations</td>
</tr>
<tr>
<td><strong>Anoro Ellipta</strong></td>
<td>COPD</td>
<td>1 puff daily</td>
<td>DPI</td>
<td>• Only 5 drugs currently have clinical data to support FDA approved labeling for the reduction of COPD exacerbations: Spiriva, Advair, Breo, and Daliresp</td>
</tr>
<tr>
<td><em>(umeclidinium/vilanterol)</em></td>
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<tr>
<td><strong>Stioltto Respimat</strong></td>
<td>COPD</td>
<td>2 puffs daily</td>
<td>Respimat - Soft Mist</td>
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<tr>
<td><em>(tiotropium/olodaterol)</em></td>
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</table>
POST-TEST #1

Which drug is indicated for asthma and COPD?

A. Stiolto Respimat
B. Seebri Neohaler
C. Spiriva HandiHaler
D. Spiriva Respimat
ANSWER 1

D
In terms of efficacy, there is a clinical difference between the 3 drugs in the LAMA/LABA class (Utibron Neohaler, Anoro Ellipta, and Stiolto Respimat).

A. True
B. False
Answer 2

False
Breathe easy knowing there are so many similar choices.
SUMATRIPTAN
SUMATRIPTAN

Currently available as
- Tablets
- Nasal Spray
- SQ injection
  - Needle and needleless nitrogen powered jet spray

New dosage forms
- Intranasal powder in novel delivery device
- Transdermal Patch
SUMAVEL DOSEPro
(Zogenix Pharmaceuticals’ only product)

For migraine relief that can start within 10 minutes

Bring in the Pro.

*In clinical studies, relief started within 10 minutes for some patients with most achieving relief within 2 hours.
**SUMAVEL DOSEPro**

- Needle free sumatriptan injection
- Uses a burst of $N_2$ gas to blast the sumatriptan into the subcutaneous tissue.
- The entire dose is injected in under 0.1 second, accompanied by a disconcerting loud “burst.”
- Sumatriptan via needle is pushed in over 5 seconds

<table>
<thead>
<tr>
<th>Local site reactions Sumavel vs sumatriptan injection</th>
<th>1 Hour post injection</th>
<th>Sumavel (n=243)</th>
<th>Sumatriptan Inj (n=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>7%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>72%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>53%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

Swelling lasted up to 8 hours post injection
Erythema lasted up to 24 hours post injection
SUMAVEL DOSEPRO

Clinical Studies

- All studies used for FDA approval were the original 2002 studies that GSK used to gain approval for the needle form of Imitrex. No specific efficacy studies were performed for Sumavel.
**SUMAVEL DOSEPRO**

- **Pros**
  - Neato no-needle device with a laser drilled hole and eco friendly nitrogen gas
  - “Only 3 steps to injection, vs. 17 steps with sumatriptan.” Snap, Flip, Press
  - Cool product slogans like “say hello to the Pro” and “bring in the Pro”

- **Cons**
  - More expensive than sumatriptan injection (needle)
  - More injection related trauma

**Phil’s take on this one:**
*Indicated for the affluent, needle-phobic migrainer who can handle the rather significant local trauma of this needle-free device.*
ONZETRA XSAIL

IF YOUR migraine IS HERE, WHY ONLY SEND treatment HERE?

Send medication directly to the back of the nose with a new Breath Powered® delivery system

Learn why the nose matters ›
ONZETRA XSail

The back of the nose may be a good place to send medicine

NASAL VALVE

Your nasal valve is a dynamic area in your nose that’s shaped like a small triangle. It helps you breathe air in while keeping foreign particles out. It has a good purpose, but may limit how well medication is delivered through your nose.

The ONZETRA™ Xsail™ nosepiece widens the nasal valve, helping medication reach the back of your nose.

YOUR NOSE IS MADE OF VALVES AND CAVITIES

POSTERIOR NASAL CAVITY

Your nose is divided into two cavities. The anterior cavity at the front helps protect your lungs from particles that enter your nose. The posterior nasal cavity in the back of your nose may help absorb things, like medication. It is rich in blood vessels and absorbent tissue, which may help deliver medication into the bloodstream.
Onzetra XSail

- Made by Avanir Pharmaceuticals
  - Their only other product is Nuedexta, a combination of dextromethorphan and quinidine
  - Treats (PBA) pseudobulbar affect
Onztra XSail

- Active ingredient: sumatriptan
- Device: all new “XSail” device that allows you to blow powder up your nose
  - No, really!
Onzetra Xsail

- Dose: 22mg
  - Each dry powder capsule contains 11mg sumatriptan. Given as “11mg” blown into each nostril.
    - In clinical trials, the actual amount delivered was 7.5mg to 8.1mg, and depends on expiratory flow rate
    - In vitro testing showed a delivery of 10mg at 30 L/min for 4 seconds

- Max dose per day: 44mg (4 nostril blows)

- Directions:
  - Remove a disposable nosepiece from foil pouch, click onto the reusable nose-blower device.
  - Press and release the piercing button to puncture the medication capsule in the nosepiece
Onzatra Xsail

Directions:
- Insert the nosepiece fully into the nose, make a tight seal
- Keeping it in your nose, rotate the mouthpiece and place in your mouth
- Blow forcefully into the device to blow the sumatriptan deep into your nose.
- If you hear a vibration and rattling noise, you did it hard enough.
ONZETRA XSAIL

- Directions:
  - Remove the nosepiece, replace with another, and blow powder into the other nostril
  - Don’t blow out of your nose while exhaling into the device.
    - It may explode?
Onzeta XSail

- Adverse events
  - Abnormal taste
    - 20%
  - Nasal discomfort
    - 11%
      - "Limited examinations of the nose and throat did not reveal any clinically noticeable injury in these patients."
  - All the usual warnings and adverse events associated with triptan use
Onzetra XSail

Clinical efficacy

- One trial was conducted to evaluate the efficacy of Onzetra XSail.
- TARGET study
- Multicenter, randomized, DB, PC study
- Compared Onzetra to placebo device in patients with moderate to severe migraine HA
- HA relief was assessed at 15, 30, 60, and 90 minutes, and 2, 24, and 48 hours after treatment
ONZETRA XSAIL

- Clinical efficacy
  - Results
    - More patients got migraine relief in the sumatriptan group than the placebo group
    - 68% vs. 45% got HA relief at 2 hours
  - What is the NNT?
    - A) 2
    - B) 4
    - C) 23
    - D) 100
ONZETRA XSAIL

- Clinical efficacy
  - Results
    - There was not a statistically significant difference in the presence of nausea, photo/phonophobia compared to placebo

- Cost
  - 8 doses = $585 (AWP) ($73 per dose)

- Pros
  - Contains both an “X” and a “Z”
  - Causes less swallowing of sumatriptan

- Cons
  - Somewhat more expensive than other sumatriptan products. No data suggests efficacy advantage over other triptans (including conventional nasal sumatriptan)
ZECUITY (SUMATRIPTAN)

Top View
- Fabric
- Activation Button
- Plastic Dome
- Batteries

Bottom View
- Foam
- Adhesive
- Electrodes

Diagram showing the device with labels for different components.
ZECUITY (SUMATRIPTAN)

- This is a PATCH for delivering sumatriptan
  - Sumatriptan iontophoretic transdermal system
- Time to peak concentration (Tmax) = 1.1 hours
- Delivers 6.5mg of sumatriptan over 4 hours
- Directions
  - Apply to upper arm or thigh only
  - Do not apply more than two patches per 24 hours
  - Do not apply a second patch sooner than 2 hours
ZECUITY (SUMATRIPTAN)

Directions

- Assemble the patch and activate within 15 minutes
- Once applied, press the activation button. An LED light will illuminate.
- Secure with medical tape if needed
- Remove the patch after 4 hours, or when the LED light turns off
- May apply a second patch if needed, to a different site. Wait at least 2 hours.
ZECUITY (SUMATRIPTAN)

Directions

- Follow 6 steps to assemble and attach the device
- Step 1
  - Pull 2 foil tabs, exposing the medication pads
    - Must apply within 15 minutes of this step, so hurry!
- Step 2
  - Rub the foil medication pads
    - These must be properly applied to the device
    - Trace the green arrow with two fingers, three times around and around the medication pad
ZECUITY (SUMATRIPTAN)

Directions

- Step 3
  - Unfold the lift open
    - Carefully lift the package flap
- Step 4
  - Peel pads and Check
    - Peel the first part of ZECUITY TDS back from the silver liner. Lay on hard surface and repeat steps 2 and 3 if this doesn’t work.
ZECUITY (SUMATRIPTAN)

- Directions
  - Step 5
    - Apply and activate
      - Apply to upper arm or thigh, press the button
      - It should blink then turn red
      - If not, no medicine is being delivered
        - Throw the patch away
    - Patients may feel mild burning sensation within 30 seconds of activating the patch
ZECUITY (SUMATRIPTAN)

- Adverse reactions
  - Application site pain, 26%
  - Application site paresthesia, 9% (16% with placebo through the same electronic device)
  - Pruritis, discomfort, irritation, discoloration
    - Between 3-8%

- Cost
  - $347 per patch (AWP)
ZECUITY (SUMATRIPTAN)

- **Update**
  - FDA has pulled the device from the market
    - “Voluntarily withdrawn” by Teva Pharmaceuticals
  - Action cites postmarketing reports of severe pain, burning and scarring of application site
  - Teva is investigating the root cause of these adverse skin reactions
SUMATRIPTAN

- Also available as
  - Tablets 25mg, 50mg, 100mg
    - ~ $1.25 each
  - Injection
    - Imitrex 6mg vial
      - $33
    - Imitrex STATdose
      - SC auto-injector = $80
    - Alsuma
      - SC auto-injector = $120
    - Sumavel DosePro
      - jet-injector = $181
  - Nasal spray
    - 5mg and 20mg per actuation
      - $50 per dose
Sumatriptan

Also available as

- Other products containing sumatriptan
  - Treximet
    - Sumatriptan and naproxen, fixed dose combo
    - $11 per tablet
SUMATRIPTAN

- And finally……
  - Migranow Pak
    - Sumatriptan 50mg tab & Camphor-menthol Gel 4-10%
      - AWP is $3,888 each
      - #30 pack discount internet price below:

<table>
<thead>
<tr>
<th>Blink price</th>
<th>After discount</th>
</tr>
</thead>
<tbody>
<tr>
<td>$101,527.89</td>
<td>$101,517.89</td>
</tr>
</tbody>
</table>

Take $10 OFF your first medication purchase
What is the most painful way to get a dose of sumatriptan?

- A) Treximet tablets
- B) Migranow Pak
- C) Imitrex STATdose
- D) Sumavel DosePro
- E) B and D
Current Available Vaccines

For *Haemophilus influenzae* Type b (Hib) Prevention
During 1989-2000, annual incidence of invasive Hib disease in children <5 y.o. by 99% to < 1 case per 100,000 children
Estimated Incidence Below Healthy People 2020 Goal

*FIGURE 2. Estimated annual incidence* of invasive *Haemophilus influenzae* Type b infection in children aged <5 years — United States, 2000–2012

Sources: National Notifiable Diseases Surveillance and Active Bacterial Core Surveillance (ABCs) data.

* Per 100,000 population.
Hib Vaccines

• **Indication:** For active immunization for the prevention of invasive disease caused by *Haemophilus influenzae* type b.

• **Population:** children 6 weeks through 4 years of age (prior to fifth birthday) and up to 18 years of age for certain high-risk groups.

• **Minimum Age:** 6 weeks

• **Minimum Intervals:**
  – Primary Series (up to 12 months old): 4 weeks
  – Booster dose (12 months and older): 8 weeks
# Monovalent Vaccine

<table>
<thead>
<tr>
<th>Vaccine Product (Mfr)</th>
<th>Trade Name</th>
<th>Components</th>
<th>Primary Series</th>
<th>Booster Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-OMP (Merck)</td>
<td>PedvaxHIB</td>
<td>PRP conjugated to OMP</td>
<td>2, 4 months</td>
<td>12 – 15 months</td>
</tr>
<tr>
<td>PRP-T (sanofi pasteur)</td>
<td>ActHIB</td>
<td>PRP conjugated to tetanus toxoid</td>
<td>2, 4, 6 months</td>
<td>12 – 15 months</td>
</tr>
<tr>
<td>PRP-T (GSK)</td>
<td>Hiberix</td>
<td>PRP conjugated to tetanus toxoid</td>
<td>2, 4, 6 months*</td>
<td>12 – 15 months</td>
</tr>
</tbody>
</table>

PRP – polyribosylribitol phosphate; OMP – outer membrane protein

*New indication for Hiberix for use in the Primary series January 1/14/2016; however, product launch will not occur until sometime in July 2016.

In 2009, the FDA approved Hiberix under an accelerated approval process for use as a booster dose due to vaccine shortage of ActHIB.
# Combination Vaccines Containing Hib

<table>
<thead>
<tr>
<th>Vaccine Product (Mfr)</th>
<th>Trade Name</th>
<th>Components</th>
<th>Primary Series</th>
<th>Booster Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRP-OMP-HepB (Merck)</td>
<td>Comvax All NDCs Inactive as of 3/10/16 - product discontinued</td>
<td>PRP-OMP + hepatitis B vaccine</td>
<td>2, 4 months</td>
<td>12 – 15 months</td>
</tr>
<tr>
<td>DTaP-IPV/PRP-T (sanofi pasteur)</td>
<td>Pentacel</td>
<td>DTaP-IPV + PRP-T</td>
<td>2, 4, 6 months</td>
<td>15 – 18 months</td>
</tr>
<tr>
<td>MenCY/PRP-T (GSK)</td>
<td>MenHibRix*</td>
<td>MenCY + PRP-T</td>
<td>2, 4, 6 months</td>
<td>12 – 15 months</td>
</tr>
</tbody>
</table>

DTaP – Diptheria & Tetanus Toxoids and Acellular Pertussis; IPV – Inactivated Polio Virus; MenCY – *N. meningitidis* serogroups C and Y

* MenHibRix is only recommended for routine meningococcal vaccination for infants who are at increased risk for meningococcal disease (e.g. infants with recognized persistent complement pathway deficiencies and infants who have anatomic or functional asplenia including sickle cell disease)
Interchangeability

• Monovalent Hib conjugate vaccines are considered interchangeable for both the primary as well as the booster doses

• Less data to support interchangeability of combination vaccines
  – When possible, the same combo vaccine should be used for subsequent doses.
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Strength</th>
<th>Route</th>
<th>CPT code</th>
<th>Desc</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monovalent Vaccines</strong></td>
<td></td>
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</tr>
<tr>
<td>ACTHIB</td>
<td>10 MCG/0.5</td>
<td>INTRAMUSC.</td>
<td>90648</td>
<td>Haemophilus influenzae b vaccine (Hib), PRP-T conjugate, 4-dose schedule (Code price is per dose = 0.5 mL)</td>
<td>$34.44</td>
</tr>
<tr>
<td>HIBERIX</td>
<td>10 MCG/0.5</td>
<td>INTRAMUSC.</td>
<td>90648</td>
<td>Haemophilus influenzae b vaccine (Hib), PRP-T conjugate, 4-dose schedule (Code price is per dose = 0.5 mL)</td>
<td>$12.16</td>
</tr>
<tr>
<td>PEDVAXHIB</td>
<td>7.5MCG/0.5</td>
<td>INTRAMUSC.</td>
<td>90647</td>
<td>Haemophilus influenzae type b vaccine (Hib), PRP-OMP conjugate, 3-dose schedule (Code price is per dose = 0.5mL)</td>
<td>$56.46</td>
</tr>
<tr>
<td><strong>Combination Vaccines</strong></td>
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</tr>
<tr>
<td>PENTACEL</td>
<td>15-20-5-10</td>
<td>INTRAMUSC.</td>
<td>90698</td>
<td>Diphtheria, tetanus toxoids, acellular pertussis vaccine, Haemophilus influenzae type b, and inactivated poliovirus vaccine, (DTaP-IPV / Hib) (Code price is per dose = 0.5 mL)</td>
<td>$104.23</td>
</tr>
<tr>
<td>MENHIBRIX</td>
<td>5-2.5/0.5</td>
<td>INTRAMUSC.</td>
<td>90644</td>
<td>Meningococcal conjugate vaccine, serogroups C &amp; Y and Haemophilus influenzae type b vaccine (Hib-MenCY), 4 dose schedule, when administered to children 2-18 months of age (Code price is per dose = 0.5 mL)</td>
<td>$29.35</td>
</tr>
</tbody>
</table>
Buprenorphine options for treatment of CHRONIC pain
FDA Approved for Chronic Pain

• Butrans Transdermal Patch (Purdue)
  – FDA approved 6/30/10

• Belbuca Buccal Film (Endo)
  – FDA approved 10/23/15
INDICATION

- Indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use:

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with long-acting opioid formulations, reserve for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

- Not indicated as an as-needed (prn) analgesic.
Buprenorphine MOA

- Partial agonist at mu opioid receptors
- Antagonist at kappa-opioid receptors
- Agonist at delta-opioid receptors
- Partial agonist at ORL-1 (nociceptin) receptors

The clinical utility of latter 3 to buprenorphine’s analgesic profile are unclear.
Activity at the mu-opioid receptors

• High binding affinity but with low intrinsic activity and a slow dissociation rate from the mu-opioid receptor
• Because the mu receptors are activated but not to the same extent as a full agonist, we see buprenorphine exhibit a dose-ceiling effect.
• Prolonged analgesic activity mediated by high-affinity binding and slow dissociation from CNS mu-opioid receptors.
  – Long duration of activity that lasts for ~24 to 60 hours
• Prevents other opioids from binding and will displace competing opioid agonists, precipitating withdrawal in patients on opioids
Dose-Ceiling Effect

- Analgesia
- Safety
- Abuse potential
ANALGESIA

- Agonist effects reach a ceiling at moderate doses and do not increase, even with increases in dosage
SAFETY

- The ‘ceiling effect’ *may provide a wider safety margin* vs full agonists.
- Risk for respiratory depression, even in overdose, may be less vs that with a full agonist.
- In the event of respiratory depression, higher than usual doses of opioid antagonists may be needed to reverse due to tight binding of buprenorphine to the opioid receptors;
  - naloxone effect may also be delayed (30 – 60 min)
  - monitor for respiratory depression for the next 24 hours
- Slow dissociation rate may attenuate withdrawal between doses or when it is d/c, due to long duration of action and ‘self-tapering’ effect.
- May cause less hormonal effects (e.g. suppression of gonadotropin production and sexual dysfunction) than full agonists.
ABUSE POTENTIAL

- Buprenorphine *may have less abuse potential* vs full agonists due to the ‘ceiling effect’.
- As the dose increases, physiological and subjective effects, including euphoria, plateau.
- At high doses, buprenorphine can act as an antagonist by blocking access to the mu opioid receptors rather than activating them.
  - Effective in opioid addiction therapy b/c it antagonizes the analgesic and euphoric effects of other opioids.
ABUSE RISK IS REAL

- Buprenorphine IS misused to get high, enhance the effects of other drugs of abuse, or curb opioid withdrawal
- Buprenorphine can be crushed, snorted, or injected for a bigger, faster effect
ABUSE

Those who abuse and divert buprenorphine advise prescribers to:

- Write for small quantities
- Conduct random UA’s (buprenorphine is not on routine urine drug screens - make sure lab knows what you are looking for)
- What for early refills and for late refills
Buprenorphine for Pain vs OUD

- OUD (e.g. Bunavail, Suboxone, Zubsolv): dosed in MG
- Pain (e.g. Butrans, Belbuca): dosed in MCG
- A typical low dose of Belbuca for pain is 150mcg, but a typical low dose of Suboxone for OUD is 4mg or 4,000mcg/1mg.
- Using even the lowest dose of a buprenorphine OUD product off-label for pain has resulted in death in patients not accustomed to opioid therapy.
OTHER INFORMATION

- Buprenorphine is 25-80x more potent than morphine
- Poor bioavailability when given orally
- Dosage forms include parenteral, transdermal and SL/Buccal films
- These bypass the first-pass liver metabolism
- Bioavailability is still relatively low
  - 15% for Butrans; 46-65% for Belbuca
How Supplied

<table>
<thead>
<tr>
<th>Belbuca Buccal film (peppermint flavored):</th>
<th>Butrans Transdermal system:</th>
</tr>
</thead>
<tbody>
<tr>
<td>75mcg, 150mcg, 300mcg, 450mcg, 600mcg, 750mcg and 900mcg</td>
<td>5 mcg/hour, 7.5 mcg/hour, 10 mcg/hour, 15 mcg/hour, and 20 mcg/hour</td>
</tr>
</tbody>
</table>
### Dosing information

<table>
<thead>
<tr>
<th></th>
<th>Butrans</th>
<th>Belbuca</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose (opioid-naïve)</strong></td>
<td>5mcg/hr</td>
<td>75mcg QD or q12h</td>
</tr>
<tr>
<td><strong>Max Dose</strong></td>
<td>20mcg/hr</td>
<td>900mcg q12h*</td>
</tr>
<tr>
<td><strong>MSE of Max Dose</strong></td>
<td>80mg/d</td>
<td>160mg/d</td>
</tr>
<tr>
<td><strong>Consider alternative treatment</strong></td>
<td>MSE ≥ 80mg/d</td>
<td>MSE ≥ 160mg/d</td>
</tr>
<tr>
<td><strong>Minimum titration interval</strong></td>
<td>72 hours</td>
<td>4 days</td>
</tr>
<tr>
<td><strong>Maximum titration dose</strong></td>
<td>5mcg/hr, 7.5mcg/hr or 10mcg/hr</td>
<td>150mcg q12h</td>
</tr>
</tbody>
</table>

* Doses up to 450mcg/hr were studied in treatment naïve patients
Dosing Info, cont.

Important: Due to potential to precipitate withdrawal
• If opioid-experienced patient, the patient must be tapered to no more than 30mg MSE daily before starting treatment with starting Belbuca or Butrans

<table>
<thead>
<tr>
<th>30 mg oral MSE⁴,⁵</th>
<th>200 mg codeine</th>
<th>7.5 mg hydromorphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>=</td>
<td>12.5 mcg/hr fentanyl transdermal</td>
<td>20 mg oxycodone</td>
</tr>
<tr>
<td></td>
<td>30 mg hydrocodone</td>
<td>10 mg oxymorphone</td>
</tr>
</tbody>
</table>

Important: Risk for QTc Prolongation
• DNE 20mcg/hr patch (Butrans) or 900mcg/hr q12h (Belbuca)
Well, doc, I still have that pain in my back...
EFFECTIVENESS

- Modest efficacy vs placebo for moderate to severe chronic low back pain in opioid-naïve and opioid-experienced
- Both Belbuca and Butrans had studies that did not show efficacy greater than placebo.
- NNT in trials showing benefit vs placebo (e.g. 30% reduction in pain) was 3 to 7
NOT A PRN MEDICATION

- Belbuca as a buccal film is at risk for being misused PRN given other transmucosal analgesia is PRN (e.g. Actiq, Fentora, Subsys)
- Not fast acting
- Relatively long duration of action
- Nausea, vomiting and dizziness may be problematic
- Could precipitate opioid withdrawal if opioid history is unclear or if patient is untruthful about opioid use
### Pharmacokinetics

<table>
<thead>
<tr>
<th>Belbuca</th>
<th>Butrans</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tmax: 2.5 to 3 hours</td>
<td>• Tmax: 60 hours</td>
</tr>
<tr>
<td>• Bioavailability: 46% to 65%</td>
<td>• Bioavailability: 15%</td>
</tr>
<tr>
<td>• SS achieved prior to the 6\textsuperscript{th} dose</td>
<td>• SS achieved during 1\textsuperscript{st} application by day 3</td>
</tr>
<tr>
<td>• Metabolism: N-dealkylation by CYP3A4 to norbuprenorphine (active) and glucuronidation</td>
<td>• Metabolism: N-dealkylation by CYP3A4 to norbuprenorphine (active) and glucuronidation</td>
</tr>
<tr>
<td>• T1/2 = 27.6 +/- 11.2 hours</td>
<td>• T1/2 = ~26 hours</td>
</tr>
</tbody>
</table>
Belbuca administration

- Use tongue to wet inside of cheek or rinse moth with water.
- Apply immediately after removal from individually sealed package.
- Place yellow side of film against the inside of the cheek and hold with clean, dry fingers for 5 seconds.
- Leave the film in place until it completely dissolves. This takes ~30 minutes.
- Do not manipulate the film or eat or drink until the film is completely dissolved.
Belbuca Technology

- Belbuca utilizes Biodelivery Sciences (BDSI's) patented BioErodible MucoAdhesive (BEMA®) drug delivery technology.
  - Adhere to oral mucosa in less than 5 seconds
  - Optimize delivery across the oral mucosa
  - Completely dissolve
- This technology is also used for Onsolis (transmucosal fentanyl for BTCP) and Bunavail (buprenorphine/naloxone for OUD).
**Butrans Administration**

- Apply immediately after removal from the individually sealed pouch to upper outer arm, upper chest, upper back or the side of the chest.
- These 4 sites on each side of the body provide 8 possible application sites.
- Butrans must be rotated among the 8 sites. After removal, wait a minimum of 21 days before reapplying to the same skin site.
Butrans Transdermal Delivery System

- Butrans uses a 7-day Transdermal Matrix Technology.
- The rate at which buprenorphine is delivered is determined by the rate of buprenorphine diffusion across the skin.
- The proportion of buprenorphine mixed in the adhesive matrix is the same in each of the 5 strengths.
- The amount of buprenorphine released from each Butrans Transdermal System per hour is proportional to the active surface area of the transdermal system.
## Cost

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSING</th>
<th>COST/UNIT</th>
<th>COST PER 28 DAYS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Belbuca buccal film</strong></td>
<td>1 film BID*</td>
<td>AWP=$5.11/film (75 &amp; 150mcg)</td>
<td>$143-$705</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$8.03/film (300mcg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$10.91/film (450mcg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$11.64/film (600mcg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$12.24/film (750mcg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$12.60/film (900mcg)</td>
<td></td>
</tr>
<tr>
<td><strong>Butrans transdermal weekly patch</strong></td>
<td>1 patch weekly</td>
<td>AWP=$61.34/patch (5mcg/hr)</td>
<td>$245-$652</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$85.88/patch (7.5mcg/hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$92.01/patch (10mcg/hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$132.73/patch (15mcg/hr)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AWP=$162.89/patch (20mcg/hr)</td>
<td></td>
</tr>
</tbody>
</table>

*Once-daily dosing only recommended in opioid-naïve patients when initiating with 75mcg.
PLACE IN THERAPY

- Moderate to severe pain requiring ATC opioid tx
- Opioid-naïve
- Opioid-experienced
  - MSE/d <160mg Belbuca
  - MSE/d <80mg Butrans
- Those at greater risk for respiratory depression (e.g. COPD, sleep apnea)
- Those at greater risk for abuse
Which of the following medications are FDA approved to treat chronic pain?

A. Bunavail
B. Zubsolv
C. Belbuca
D. Suboxone
POST-TEST

Which of the following medications are FDA approved to treat chronic pain?

C. Belbuca