Pharmacy Benefit Determination Policy

Policy Subject: Hereditary Angioedema Agents
Policy Number: SHS PBD21
Category:
Policy Type: ☒ Medical ☐ Pharmacy
Department: Pharmacy

Dates:
Effective Date: October 28, 2010
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Next Review Date: October 2017

Product (check all that apply):
☒ Group HMO/POS
☒ Individual HMO/POS
☒ PPO
☒ ASO

Clinical Approval By:
Medical Directors
PHP: Peter Graham, MD; SPHN: Harman Nagler, MD
Pharmacy and Therapeutics Committee
PHP: Peter Graham, MD; Sparrow ASO: Harman Nagler, MD

Policy Statement:
Physicians Health Plan, PHP Insurance & Service Company, and Sparrow PHP will cover Hereditary angioedema agents through the Medical Benefit based on approval by the Clinical Pharmacist or Medical Director using the following determination guidelines

Drugs and Applicable Coding:
J-code: Cinryze - J0598; Berinert - J0597, J1290; Kalbitor - J2425; Firazyr - 014778; Ruconest - J0596

Clinical Determination Guidelines:
Document the following with chart notes

A. Hereditary Angioedema (HAE) Diagnosis
   1. Signs & Symptoms (S & Sx)
      a. Swelling: Any body part, extremities, face, trunk, GI tract, GU regions or upper airways.
      b. Abdominal Sx (mimics colic or acute appendicitis/abdomen): N/V, abd. pain, diarrhea.
      c. Laryngeal Sx: Rare at < 3 yo age; occurs later than other symptoms.
      d. Sx worsen w untreated attacks: Prolonged, ↑ during 24 hrs & ↓ at 48-72 hrs.
   2. Attack triggers: Stress, minor trauma, menstruation, pregnancy, infections or some drugs (estrogen-containing pills or HRT).
   3. Lab test: C4, C1-INH & functional levels

B. Acute Treatment for Attacks
   1. On demand treatment:
      a. All HAE pts w C1-INH deficiencies have medication on hand for acute attacks.
      b. Treat home & train to self-administer.
   2. Treat as soon as an attack is clearly recognized regardless of location.
   3. Laryngeal symptoms: Immediately go to the hospital if sx persist after initial treatment
4. Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Ind</th>
<th>Dosage</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berinert plasma-derived C1 INH</td>
<td>Acute Attacks</td>
<td>20 U/KG IV</td>
<td>Inhibits kallikrein, factors XIIa/XIa, C1s, Cir, MASP-1, MASP-2 &amp; plasmin</td>
</tr>
<tr>
<td>Ruconest recombinant C1 INH</td>
<td>Acute Attacks</td>
<td>&lt; 84 Kg: 50 U/KG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 84 Kg: 4,200U</td>
<td>May repeat X1</td>
</tr>
<tr>
<td>Kalbitor ecallantide</td>
<td>Acute Attacks</td>
<td>30mg SQ (3 x 1mL)</td>
<td>Inhibits plasma Kallikrein</td>
</tr>
<tr>
<td>Firazyr icatibant</td>
<td>Acute Attacks</td>
<td>30mg SQ</td>
<td>Bradykinin B2 receptor antagonist</td>
</tr>
</tbody>
</table>

C. Short-Term Prophylaxis
1. Minor procedures: No tx. (w C1 Inhibitor on hand) or Danazol 200mg 3x/day x 5-7 days pre & 2 days post.
2. Major Procedures: Berinert: 20U/Kg 1 hr. pre surgery & daily until no risk of angioedema; Danazol; or fresh frozen plasma

D. Long-Term Prophylaxis
1. Indication: Failure of on demand therapy (> 24 days/yr w sx or > 12 severe attacks/yr.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
<th>HAE Ind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danocrine danazol</td>
<td>200mg/day (100mg/3d - 600mg/d)</td>
<td>50mg/day (50mg/wk - 200mg/d)</td>
<td>Yes</td>
</tr>
<tr>
<td>Winstrol stanozolol</td>
<td>2mg/d (1mg q 3d - 6mg/d)</td>
<td>5mg/day (0.5mg/wk - 2mg/d)</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxandrin oxandroalene</td>
<td>10mg/day (2.5mg/3d - 20mg/d)</td>
<td>0.1mg/Kg/day (2.5mg/wk - 7.5mg/d)</td>
<td>No</td>
</tr>
<tr>
<td>Android methyltestosterone</td>
<td>10mg/day (men only)(5mg q 3 d - 30mg/d)</td>
<td>Not recommended</td>
<td>No</td>
</tr>
</tbody>
</table>

| Antifibrolitics                             |                   |                  |         |
| Ámicanor caproic acid                      | 2g 3x/day (1g 2x/d - 4 g 3x/d) | 0.05g/Kg BID (0.025g/Kg/2x/d - 0.1g/kg 2x/d) | No     |
| Transexamic acid (Lysteda,)                | 1g 2x/day (0.25g 2x/d - 1.5g 2x/d) | 20mg/Kg 2x/day (10mg/Kg 2x/d-25mg/Kg/3x/d) | No     |

| C1 INH                                     | 1000U IV q 3-4 d  | NA               | Yes     |
### Appendix I: Monitoring & Patient Safety

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Reactions</th>
<th>Monitoring</th>
<th>REMS</th>
</tr>
</thead>
</table>
| Berinert Cinryze plasma C1-INH | • CNS: HA (17%)  
• GI: Nausea (18%)  
• Pregnancy category C | • CV: S & Sx thrombolytic events  
• Immunologic: S & Sx hypersensitivity  
• Self-life: 30mons. | Not needed |
| Kalbitor ecallantide | • CNS: HA (8-16%), fatigue (12%)  
• GI: Nausea (5-13%), diarrhea (4-11%)  
• Immunologic: Antibody development (IgE: 5-20%, neutralizing: 9%)  
• Pregnancy category C | • Immunologic: S & Sx hypersensitivity | REMS program discontinued by FDA April 5, 2013 |
| Firazyr icatibant | • Misc.: Injection site reactions (97%),  
• Pregnancy :Category C | • Symptoms relief laryngeal sx/airway obstruction  
• Self-life: 2 yrs | Not needed |
| Ruconest recombinant C1 INH | • CNS: HA (>10%)  
• GI: Abdominal pain (>12%)  
• Resp.: Oropharyngeal (>12%) | • CV: S & Sx thrombolytic events  
• Misc: S & Sx hypersensitivity  
• Self-life: 48 mons. | Not Needed |
| Danocrine danazol Winstrol stanozolol Oxandrin oxandrolone Android methyl-testosterone | • Androgenic: acne, edema, hirsutism, altered voice, oily skin/hair, seborrhea, hair loss  
• CNS: Dizziness, HA, emotional liability, benign intracranial HTN (black box), fainting, weakness  
• CV: HTN,TE (Black Box)  
• GI: Gastroenteritis, N/V, constipation  
• GU: Hematuria, prolonged amenorrhea  
• Hem: ↑ RBC/Plt,erythrocytosis, leukocytosis  
• MS: muscle cramps/spasms, joint pain/swelling  
• Misc: Libido change, chills, fever  
• Pregnancy category X (black box) | • CNS: S & Sx of intracranial HTN  
• Endo/metab: Androgenic changes  
• Labs: LFT’s, renal fx, Lipoproteins | Not Needed |
| Amicar aminocaproic acid Lysteda tranexamic acid | • CV: Bradycardia, hypotension  
• CNS: Confusion, convulsions, dizzy  
• Derm: Pruritis, rash  
• GI: Diarrhea, N/V, abdominal pain  
• GU: renal failure  
• Hem: agranulocytosis, coag disorder  
• MS:CPK increase, myalgia, myopathy  
• Resp.: Dyspnea, PE  
• Misc: allergy/hypersensitivity Rx, edema  
• Pregnancy category C | Amicar  
• Lab: Fibrinogin, CPK, BUN Cr  
Lysteda  
• CNS: S & Sx seizures  
• CV: TE  
• Opthal: Eye exam pre & during | Not needed |
Pharmacy Benefit Determination Policy

References and Resources:

10. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration Int Arch Allergy Immunol. 2013;16(suppl 1):3-9

Approved By:

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Human Resources Michelle Leach, HR Manager 10/26/16