BERINERT (human C1 esterase inhibitor), CINRYZE (human C1 esterase inhibitor), FIRAZYR (icatibant), RUCONEST (conestat alpha), hereditary angioedema medicines

High clinical benefit in their respective indications, but no demonstrated clinical advantage, with the exception of BERINERT in adults, adolescents and children, and FIRAZYR in adults, representing a moderate clinical added value for the management of acute hereditary angioedema attacks.

Main points

BERINERT, CINRYZE, FIRAZYR and RUCONEST have been granted an MA for the treatment of acute hereditary angioedema attacks (HAE) and/or for short-term and/or long-term prevention in children, adolescents and adults, according to their respective MAs.

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<th>Treatment of acute attacks</th>
<th>Short-term prevention</th>
<th>Long-term prevention</th>
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<tr>
<td>CINRYZE</td>
<td>(children, adolescents, adults)</td>
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<td>BERINERT</td>
<td>(paediatrics, adults)</td>
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<td>FIRAZYR</td>
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<tr>
<td>RUCONEST</td>
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Subcutaneous administration of FIRAZYR, with self-administration by the patient possible after learning, presents a benefit relative to IV administration, particularly when used in an emergency context. Its short plasma half-life may require a second injection. BERINERT and CINRYZE, administered IV, have longer half-lives, respectively of 36 and 56 h, than those of FIRAZYR and RUCONEST.

RUCONEST may contain traces of rabbit protein, thus requiring precautions prior to its use, though it is administered in an emergency context.

Therapeutic strategy

- Hereditary angioedema is characterised by transient (48 to 72 hours) and recurrent subcutaneous and/or sub-mucosal edema. The disease may occur at any age, though more frequently during childhood and adolescence. Edema may affect the digestive tract, leading to a sub-occlusive syndrome causing significant pain or even, more rarely, hypovolaemic shock. Laryngeal involvement may be life-threatening.
- In children, most HAE attacks occur with no triggering factor. The most frequently reported triggers include mechanical trauma, psychological stress and airway infection. Teething and some medicinal products, such as ACE inhibitors, may trigger these attacks.
- Suppression of identifiable triggers is the first measure to take to prevent attacks. Short-term treatment of moderate HAE attacks relies on tranexamic acid (EXACYL, off-label). Corticosteroids are ineffective. The C1 esterase inhibitors that may be used to treat severe attacks, in particular laryngeal ones, are BERINERT, CINRYZE, FIRAZYR and RUCONEST. These medications are more effective when administered promptly following onset of the first symptoms of the attack.
- Before any intervention requiring a minor invasive procedure, it is not advisable to initiate preventive treatment, but rather to treat any attack that may occur. In the event of minor intervention, the following short-term prophylactic treatments may be considered: administration of danazol 600 mg/day per os 5 days before the...
procedure and 5 days after, combined with tranexamic acid 1 g x 3/day per os, starting on the eve of the procedure and continued the following day. Danazol is contraindicated however in pregnant or breast-feeding women and should be avoided in children. Moreover, it is not a treatment of choice in women due to its adverse effects related to its androgenic effect.

- Routine therapy (long-term and regular prophylaxis) is based on the administration of macroprogestative contraception in women, or of tranexamic acid (off-label), or of danazol (DANATROL) which is not recommended in children and women in light of its androgenic effects.

- **Place in the therapeutic strategy**
  Management of HAE attacks in adults and adolescents relies on the administration either of subcutaneous icatibant (FIRAZYR), or of slow IV human plasma C1 inhibitor concentrate (BERINERT, CINRYZE), or its recombinant alternative (RUCONEST). BERINERT, CINRYZE (2 years old and above) and FIRAZYR (aged 2 years and older) may be used in children to treat severe attacks, in particular laryngeal ones.
  
  The characteristics of conestat alfa (RUCONEST), extracted from transgenic doe milk and which may contain traces of rabbit protein, requires that patients be questioned concerning prior exposure to rabbit proteins and informed of the signs and symptoms suggestive of an allergic reaction. This must be taken into consideration in the context of emergency administration, thus meaning that it should not be used as a first-line treatment if an alternative is available.
  
  In the event of an intervention involving the upper respiratory tract, particularly dental care, or that may cause tissue damage leading to oedema, preventive use of a C1 esterase inhibitor is recommended: BERINERT or CINRYZE (2 years old and above).
  
  CINRYZE, for which efficacy in terms of reduction of the number of attacks in the context of routine prevention (long-term prophylaxis) of angioedema attacks has been demonstrated, has a place in the therapeutic strategy as a basic treatment.
  
  There is a risk of supply shortage for C1 esterase inhibitors (CINRYZE and BERINERT), with resulting consequences on morbidity and mortality.

**Clinical data**

- Concerning BERINERT, in a 24-month follow-up study, 1,085 attacks occurring in 57 patients were treated with BERINERT. The median time between BERINERT administration and improvement of symptoms was of 0.46 hours per patient and of 0.37 per attack, for all attack types.
  
  Concerning CINRYZE in the attack treatment, a study showed a significant decrease in the median time to relief of symptoms with CINRYZE (2 hours [0.8 – NA]) versus placebo (> 4 hours [2.0 – NA]), HR = 2.407 [1.171; 4.948]. In another study, the number of monthly attacks dropped from 4.7 upon inclusion to 2.0 upon inclusion to 0.5 after a mean treatment duration of 6 months. Considering the methodology of this study (before-after descriptive), care should be taken when interpreting these results. In the prevention of acute attacks, a study conducted over two periods of 12-weeks showed a significant reduction in the number of attacks with CINRYZE versus placebo: 6.1 (± 5.43) attacks, versus 12.7 (± 4.8) attacks, p<0.001.
  
  Concerning FIRAZYR, the publications listed in the IOS international register about real life use of FIRAZYR are in favour of its efficacy and do not reveal any particular tolerance signals. Most attacks required only one injection of FIRAZYR (87.2% of attacks treated by self-administration versus 91.9% of attacks treated by administration by a healthcare professional). Among the HAE attacks treated by self-administration, 12.8% required an administration of a second or third injection, compared to 8.1% of attacks treated by a healthcare professional.
  
  Concerning RUCONEST, in one study focusing on attack treatment in 75 patients, the median time to improvement of symptoms at the location of the first attack was significantly shorter in patients treated with RUCONEST (90 minutes) compared to those treated with a placebo (152 minutes), p<0.031.
  
  There are no direct or indirect comparisons of these medicinal products. The available tolerance data do not show any particular signals.

**Special prescription requirements**

- Medicinal products subject to hospital prescription.

**Benefit of the medicinal product**

- The actual clinical benefit* of BERINERT, CINRYZE, FIRAZYR and RUCONEST is high in the indications of their respective MAs.
  
  BERINERT provides a moderate improvement in actual clinical benefit** (IACB III) for the management of hereditary angioedema attacks in adults and children, like FIRAZYR in adults, and BERINERT does not provide...
any improvement in actual clinical benefit (IACB V) over the treatment available in the short-term prevention strategy for acute HAE attacks before intervention.

- CINRYZE does not provide any improvement in actual clinical benefit** (IACB V), in adults, adolescents and children, for the management of acute angioedema attacks, for the pre-procedure prevention of angioedema attacks, or for the routine prevention of severe and recurrent hereditary angioedema attacks.

- FIRAZYR does not provide any improvement in actual clinical benefit** (IACB V) for the management of acute angioedema attacks in adolescents and children aged 2 years and older and, like BERINERT, FIRAZYR provides a moderate improvement in actual clinical benefit** (IACB III) for the management of acute angioedema attacks in adults.

- RUCONEST does not provide any improvement in actual clinical benefit** (IACB V) over other treatments for acute HAE attacks available for adults and adolescents.

- Approval for hospital treatment.

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement".