20th Expert Committee on Selection and Use of Essential Medicines

Peer Review Report #2

Plasma-derived C1 esterase inhibitor (human)

(1) Does the application adequately address the issue of the public health need for the medicine?

Yes □  No √ □

The evidence submitted is inadequate with regard to the public health need for the medicine

As per the application,
1. Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder.
2. The prevalence of HAE is estimated to be approximately 1 in 50,000 persons, with no major differences due to ethnicity or gender being reported. The range of prevalence is 1:50,000-150,000 (References 1-4)
3. Recent reports: Lower prevalence of HAE in Asia (ranging from 0.1 to 9.4 in 1,000,000 inhabitants) than in Europe and North America (ranging from 0.4 in 100,000 to 1 in 50,000 inhabitants) – this lower prevalence in Asia may be due to under diagnosis
4. The product can be considered as an orphan drug since it satisfies the criteria for orphan drug designation
   • When the prevalence is less than 5 (EU) -7.5 (USA)/10,000
   • HAE is about 0.2/10,000 (considering 1:50,000 prevalence)
   • This product also fulfills some other criteria for orphan drug status as well

(2) Have all important studies that you are aware of been included in the application?

Yes √ □  No □

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

Yes □  No √ □

The Hereditary angioedema international working group (HAWG) published its consensus report on Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 in 2012 (Reference 5).

Note: Most authors have declared conflicts of interest as they have been consultants/research fellow/funded by the Pharmaceutical industry manufacturing the therapeutic options for this condition.

In the studies included in this EB consensus report and Annex 2 of the application:
1. The primary outcomes for efficacy of acute treatment of this condition are mainly about time to onset of relief/clinically significant/complete relief.
2. Mostly subjective outcomes – measured in Phase III studies
3. **Mainly placebo controlled**
4. *The magnitude of clinical benefit in these subjective primary outcomes in the context of LMICs is very limited.*
5. **Three studies from the consensus report are summarized here: Some outcome indicators are not significant even when compared to placebo**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Design</th>
<th>Outcome measures</th>
<th>Time to outcome</th>
<th>Significance</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>Waytes/Kunschak et al. (6,7)</td>
<td>pdC1-INH</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>Time to relief (h)</td>
<td>7.62 (7.08)</td>
<td>P = 0.007</td>
<td>Complete resolution – not significant</td>
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<td></td>
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<td>Time to resolution (h)</td>
<td>23.98 (14.81)</td>
<td>P = 0.09</td>
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<tr>
<td>Craig et al. (8)</td>
<td>pdC1-INH</td>
<td>Parallel-group randomized, double-blind placebo-controlled</td>
<td>Time to onset of relief (h)</td>
<td>0.5 (0.17–24) vs 1.17 (0.17–24)</td>
<td>P = 0.2731</td>
<td>10 Unit – non significant</td>
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<tr>
<td></td>
<td>(Berinert_)</td>
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<td>1.5 (0.2–24) vs 4.92 (0.47–1486) vs 20 (0.47–1486) vs 7.79 (0.33–1486)</td>
<td>P = 0.0025</td>
<td>20 U units significant</td>
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<td></td>
<td></td>
<td>P = not reported</td>
<td>P = 0.237</td>
<td>Complete resolution – not significant</td>
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<tr>
<td>Zuraw et al. (9)</td>
<td>pdC1-INH</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>Time to onset of relief (h)</td>
<td>2 vs &gt;4</td>
<td>P = 0.0</td>
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<td></td>
<td>(Cinryze)</td>
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</table>

(4) *Is there evidence of efficacy in diverse settings and/or populations?*

Yes ☐  No ✓

Three key consensus statements were unanimously agreed upon (as per the consensus report):

1. **Reducing morbidity and mortality in HAE must begin with early and accurate diagnosis.**
2. **HAE patients should have a specialist familiar with the disease involved in their care.**
3. **Treatment for HAE must be individualized to patient’s needs and request to provide optimal care and restore a normal quality of life to the patient.**

- In most LMICs, none of the above (especially the first 2) will be available. No evidence about efficacy of these therapeutic options in LMICs where these facilities are not available
• Even the consensus report accepts the limitations: (Reference 5)

“Clinical trials were necessarily designed to investigate efficacy in a relatively limited situation, namely timely treatment for established attacks, and with relatively limited outcomes. Therefore, they may not directly reflect ‘real life’ where symptoms are treated early or at prodromes and final outcomes are measured by quality of life, economic well-being, and cost-effectiveness”

(5) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☑ ☐ No ☐

• Application has considered the safety and adverse effects
• There are adverse effects of concern and adverse effects that may require special monitoring (allergic reactions and transmission of blood borne infections, etc)
• In LMICs, risk versus benefit assessment does not favour this drug to be included in EMLs
• It is anyway approved in Europe for self-administration to treat all acute attacks and in USA to treat facial and abdominal attacks – but situation in LMICs would be very much different

ADDITIONAL CONSIDERATIONS:

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

Yes ☐ No ☑

See comments given for question 4

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☑ ☐ No ☐

As per the available documents, the product is not registered in most of LMICs

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☐ No ☑

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

1. In LMICs, it will not be cost effective to be included in EMLs
2. Individual countries could consider supply of this product for individual patient basis ("rare essentials") for acute treatment provided all other criteria are met – Orphan drug clause

3. This drug is also indicated for LTP (long term prophylaxis) – in that instance, it is 1000 IU twice a week for life long
   a. Reduces the attacks only by 50%
   b. Cost will be about 1500 USD (1000 units) into 112 (biweekly injections) per annum
   c. Cheaper options (Danazol) seem to be equally effective

But in LMIC in the context of absence of national medicinal policy, hidden and open influence by pharmaceutical industry and irrational prescribing, if included in EML, this product would be used for LTP as well which will not be cost effective at all in LMIC settings

(10) Any additional comments?

(11) Please summarise the action you propose the Expert Committee takes.

**Not to include in the WHO Model EML**

1. Prevalence is very low
2. Diagnostic and speciality treatment facilities not available in most LMICs
3. Safety issues
4. No evidence on efficacy/effectiveness in LMIC settings
5. No evidence on cost effectiveness in LMIC settings
6. Outcome indicators are “explanatory” attitude and not “pragmatic”