**TRANSPARENCY COMMITTEE**

Opinion  
19 February 2014

**BERINERT 500 IU, powder and solvent for solution for injection/infusion**  
10 ml glass vial with transfer device and syringe, alcohol swabs (2) and plaster  
(CIP: 34009 574 596 3 5)

Applicant: CSL Behring SA

<table>
<thead>
<tr>
<th>INN</th>
<th>C1-esterase inhibitor, human</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2012)</td>
<td>B02AB03 (C1-esterase inhibitor)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Extension of indication</td>
</tr>
<tr>
<td>List concerned</td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
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<tr>
<td>Indication concerned</td>
<td>“Hereditary angioedema type I and II (HAE). [...] pre-procedure prevention of acute episodes.”</td>
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</table>

The legally binding text is the original French version.
| **AB** | The actual benefit of BERINERT is substantial in this extension of the indication to the short-term pre-procedure prevention of acute HAE episodes. |
| **IAB** | For the short-term pre-procedure prevention of acute HAE episodes, BERINERT does not provide any improvement in actual benefit (IAB V, non-existent) over other treatments already available. |
| **Therapeutic use** | This proprietary medicinal product is a first-line therapy in the short-term preventive treatment of acute HAE attacks. |
| **Recommendations** | |
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (procedure) | Initial date (mutual recognition, rapporteur state: Germany): 19/03/2009  
Date of extension of the indication: 2/08/2013 |
|------------------------------------|-------------------------------------------------------------------------|
| Prescribing and dispensing conditions/special status | List I  
Medicine for hospital prescription |
| ATC Classification | 2012  
B Blood and blood-forming organs  
B02 Other medicinal products used in haematology  
B02A Other medicinal products used in haematology  
B02AB Proteinase inhibitors  
B02AB03 C1-inhibitor |

02 BACKGROUND

This is an application for inclusion in an extension of the indication to “pre-procedure prevention of acute hereditary angioedema (HAE) episodes”.

The active ingredient of BERINERT, human C1-esterase inhibitor, is obtained by extraction from plasma.

BERINERT is already indicated in the treatment of acute HAE episodes; this indication was examined by the Transparency Committee on 08/07/2009.

03 THERAPEUTIC INDICATIONS

“Hereditary angioedema type I and II (HAE). Treatment and **pre-procedure prevention** of acute episodes.”

04 DOSAGE

“Pre-procedure prevention of angioedema attacks: 1000 IU less than 6 hours prior to a medical, dental, or surgical procedure.

**Children:** Pre-procedure prevention of angioedema attacks: 15 to 30 IU per kilogram body weight (15-30 IU/kg b.w.) less than 6 hours prior to a medical, dental, or surgical procedure. Dose should be selected taking into account clinical circumstances (e.g. type of procedure and disease severity).”
HAE is characterised by episodes of subcutaneous and/or submucosal oedema that are transient (48-72 hours) and recurrent. The disease can manifest itself at any age but is most common during childhood and adolescence.

The oedema may affect the digestive tract and produce a pseudo-occlusive syndrome responsible for severe pain that is sometimes associated with ascites and hypovolaemia. Involvement of the larynx can be life-threatening.

HAE type I and II are due to different alterations to the C1-esterase inhibitor (C1-INH) gene: deletion or poor transcription for type I and mutation for type II. The diagnosis of type I and II HAE is based on C4 and C1-INH assays. Oedema is triggered by increased vascular permeability due to release of excess bradykinin brought on by C1-INH inhibitor deficiency.

Current treatment is based on:
- basic treatment with DANATROL (danazol) to prevent attacks,
- suppression of identifiable triggering factors (foods, medicinal products such as angiotensin-converting enzyme inhibitors, etc.),
- short-term treatment of attacks:
  - treatment of moderate attacks is based on tranexamic acid (EXACYL, use without Marketing Authorisation);
  - treatment of severe (laryngeal) attacks is based on intravenous administration of a C1-INH concentrate (BERINERT, CINRYZE or RUCONEST) or on subcutaneous administration of icatibant (FIRAZYR).

The short-term prevention of HAE in patients undergoing minor surgical procedures (in particular dental surgery or surgery requiring intubation) is based on administration of:
- high doses of DANATROL (danazol), administered 5 to 7 days before the procedure,
- a C1-INH less than 6 hours before the procedure, CINRYZE, which is the first inhibitor to have been granted Marketing Authorisation in the prevention of HAE attacks.

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**06 CLINICALLY RELEVANT COMPARATORS**

### 06.1 Medicinal products

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Same TC*</th>
<th>Indication</th>
<th>Date of opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursement</th>
<th>Medicinal products indicated in the short-term prevention of HAE attacks</th>
</tr>
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<tbody>
<tr>
<td>CINRYZE (human C1-esterase inhibitor Viropharma SAS)</td>
<td>Yes</td>
<td>“Treatment and <strong>pre-procedure prevention</strong> of angioedema attacks in adults and adolescents with hereditary angioedema (HAE). Routine prevention of angioedema attacks in adults and adolescents with severe and recurrent attacks of hereditary angioedema (HAE) who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeated acute treatment.”</td>
<td>20/06/12</td>
<td>Substantial</td>
<td>In the management strategy for HAE, CINRYZE does not provide any improvement in actual benefit (IAB V) over other treatments already available.</td>
<td>Yes</td>
<td></td>
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<tr>
<td>DANATROL (danazol) Sanofi-Aventis France</td>
<td>No</td>
<td>Hereditary angioneurotic oedema</td>
<td>07/01/09</td>
<td>Substantial</td>
<td></td>
<td>Yes</td>
<td></td>
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</tbody>
</table>

**For information, the medicinal products indicated or used in the treatment of HAE attacks**

<table>
<thead>
<tr>
<th>NAME (INN) Company</th>
<th>Same TC*</th>
<th>Indication</th>
<th>Date of opinion</th>
<th>AB</th>
<th>IAB (Wording)</th>
<th>Reimbursement</th>
<th>Medicinal products indicated in the short-term prevention of HAE attacks</th>
</tr>
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<tbody>
<tr>
<td>RUCONEST (recombinant C1-esterase inhibitor)</td>
<td>Yes</td>
<td>RUCONEST is indicated in the treatment of acute attacks of angioedema in adults with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.</td>
<td>9/03/11</td>
<td>Substantial</td>
<td>In adults with hereditary angioedema (HAE) caused by C1-esterase inhibitor deficiency, RUCONEST does not provide any improvement in actual benefit (IAB V) over other treatments for acute HAE attacks already available (FIRAZYR, BERINERT).</td>
<td>Yes</td>
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<td>FIRAZYR (icatibant)</td>
<td>No</td>
<td>FIRAZYR is indicated for symptomatic treatment of acute attacks of hereditary angioedema in adults (with C1-esterase-inhibitor deficiency).</td>
<td>29/10/08</td>
<td>Substantial</td>
<td>FIRAZYR provides a minor improvement in actual benefit (IAB IV) in the management of hereditary angioedema attacks.</td>
<td>Yes</td>
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<td>EXACYL (tranexamic acid)</td>
<td>No</td>
<td>Use without Marketing Authorisation</td>
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<td>No</td>
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*therapeutic category

### 06.2 Other forms of treatment

The suppression of identifiable triggering factors such as certain foods, certain medicinal products (ACE inhibitors, etc.) forms part of the management of this pathology.

**Conclusion:** The clinically relevant comparators are CINRYZE and DANATROL.
07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Information on reimbursement of the medicinal product in the extension of the indication examined in this Opinion.

<table>
<thead>
<tr>
<th>Country</th>
<th>Reimbursement</th>
<th>Scope (indications) and special condition(s)</th>
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<tbody>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>Hereditary angioedema (HAE) type I and II. Treatment of angioedema attacks and prevention prior to medical, dental or surgical procedures.</td>
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<tr>
<td>Austria</td>
<td>Yes</td>
<td>Congenital angioedema: Treatment of acute episodes and pre-procedure prevention.</td>
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<td>Belgium</td>
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<td>Switzerland</td>
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08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The data submitted by the company in support of its application are based on a literature review; there are currently no specific clinical studies examining the efficacy of BERINERT in the short-term prevention of HAE attacks before surgical procedures.

The data supplied are:
- A retrospective study that sought to compare the number of HAE episodes occurring after dental extractions in patients pretreated and not pretreated with a C1-esterase inhibitor (Bork 2011).
- A pooled analysis of two studies investigating CINRYZE in the short-term prevention of HAE attacks in surgical, dental or medical procedures, for which only an abstract is available (Lumry 2011). This study is therefore not discussed in this Opinion.
- Case reports on 15 patients who had undergone dental or surgical procedures. Case studies do not constitute evidence and are therefore not taken into account.

Bork study (2011)
This study concerned 171 patients followed up in a dermatology department in Germany who were questioned a posteriori about the number of HAE attacks occurring after a dental extraction. Patients who had undergone more than one dental extraction may or may not have received short-term prophylaxis, depending on the extraction. Some patients were consequently included more than once; the analysis was carried out on 196 patients: 148 without prophylaxis and 48 with short-term prophylaxis based on C1-INH esterase at doses of 500 or 1000 IU.

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Results:
HAE attacks were observed in 55/148 patients (37.2%) without prophylaxis versus 10/48 (20.8%) in patients with C1-INH prophylaxis; no statistical test available.
Oedema was observed in 124/577 (21.5%) of procedures without prophylaxis versus 16/128 (12.5%) procedures with C1-INH pre-treatment, p < 0.035.
This difference was significant only in the group treated with a dose of 1000 IU, but not in the group treated with doses of 500 IU.

In view of the methodology of this study, results that are purely exploratory should be interpreted with caution and need to be confirmed by clinical studies.

08.2 Safety/adverse effects

According to the SPC, the most common adverse effects, observed in rare cases (≥ 1/10,000 and < 1/1000), are: allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, redness, urticaria, dyspnoea, headache, dizziness, nausea), fever, reactions at the injection site.

These adverse effects do not vary according to indication.

Viral safety:
The active ingredient of BERINERT, human C1-esterase inhibitor, is obtained by extraction from plasma.

According to the SPC, “Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
The measures taken are considered effective for enveloped viruses such as HIV, HBV, HCV and for the non-enveloped viruses HAV and parvovirus B19.
Appropriate vaccination (hepatitis A and B) should be generally considered for patients in regular/repeated receipt of human plasma-derived products.”

08.3 Summary & discussion

Principal efficacy results:
In the 2011 Bork study, HAE attacks were observed in 55/148 patients (37.2%) without prophylaxis versus 10/48 (20.8%) in patients with C1-INH prophylaxis; no statistical test available.
Oedema was observed in 124/577 (21.5%) of procedures in patients without prophylaxis versus 16/128 (12.5%) procedures in patients pretreated with C1-INH, p < 0.035.
This difference was significant only in the group treated with a dose of 1000 IU, but not in the group treated with doses of 500 IU.

In view of the methodology of this study, results that are purely exploratory should be interpreted with caution and need to be confirmed by clinical studies.

Principal safety results:
According to the SPC, the most common adverse effects, observed in rare cases (≥ 1/10,000 and < 1/1000), are: allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, redness, urticaria, dyspnoea, headache, dizziness, nausea), fever, reactions at the injection site.

For medicinal products obtained from human plasma, precautions against viral infections must be taken.
Discussion:
There have been no specific clinical studies examining the efficacy of BERINERT in the prevention of HAE attacks before surgical procedures other than dental extraction.

There are no available studies versus an active comparator, specifically danazol (DANATROL).

08.4 Planned studies
Not applicable.

09 THERAPEUTIC USE\(^1,2\)

The treatment of hereditary angioedema (HAE) is based on basic treatment with an androgen (DANATROL), long-term prevention of attacks and suppression of identifiable triggering factors (foods, medicinal products such as ACE inhibitors, etc).

For short-term treatment:
- moderate attacks are treated with tranexamic acid (EXACYL, use without Marketing Authorisation).
- for severe, in particular laryngeal, attacks, intravenous administration of a C1-INH concentrate (BERINERT, CINRYZE or RUCONEST) or subcutaneous administration of icatibant (FIRAZYR) are indicated.

Corticosteroids are ineffective.

The short-term prevention of HAE attacks in patients undergoing surgical procedures is based on the administration of:
- high doses of DANATROL (danazol) administered 5 to 7 days before the procedure,
- a C1-INH less than 6 hours before the procedure. CINRYZE is the first inhibitor to have been granted Marketing Authorisation in the short-term pre-procedure prevention of HAE attacks.

Therapeutic use of BERINERT:
BERINERT is therefore the second C1-esterase inhibitor that may be administered in this indication. The clinical data submitted, obtained with a C1-INH, are not specific to the proprietary medicinal product, represent a low level of evidence and concern only dental extraction procedures.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

010.1 Actual benefit

- Hereditary angioedema (HAE) is characterised by transient and recurring episodes of subcutaneous and/or submucosal oedema in variable localisations (cutaneous, gastrointestinal, pharyngeal, etc.). HAE is a chronic rare and disabling genetic disorder which can be life-threatening when it affects the larynx.

- This proprietary medicinal product is intended as preventive therapy.

- This medicinal product is a first-line therapy in the short-term preventive treatment of acute HAE attacks. The clinical data submitted for it concern dental extraction procedures.

- Alternative drug therapies exist, particularly in the prevention of attacks (CINRYZE and DANATROL).

- The efficacy/adverse effects ratio for this medicinal product is high.

Public health benefit:

The public health burden of patients with acute attacks of hereditary angioedema (HAE) brought on by C1-esterase inhibitor deficiency is low because of the limited number of patients. Improving the management of this disease is a public health need that is an established priority (French National Plan on Rare Diseases 2010-2014). Based on the results of clinical studies in the short-term prevention of attacks, the proprietary medicinal product BERINERT is not expected to have an impact on the morbidity, mortality and quality of life of these patients in population terms. The proprietary medicinal product BERINERT does not therefore provide any additional response to the identified need. Consequently, based on the current state of knowledge, the proprietary medicinal product BERINERT is not expected to offer any public health benefit in the short-term prevention of HAE attacks.

Taking account of these points, the Committee considers that the actual benefit of BERINERT is substantial in this extension of the indication.

Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

For short-term pre-procedure prevention of acute HAE episodes, BERINERT does not provide any improvement in actual benefit (IAB V, non-existent) over other treatments already available.

010.3 Target population

The target population of BERINERT corresponds to patients undergoing short-term pre-procedure preventive treatment for acute attacks of hereditary angioedema (HAE).
This population is included in the population of patients with HAE (original indication of this proprietary medicinal product). This extension of the indication does not result in any increase in the initial estimate of the target population, i.e. 850 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for use by hospitals in the extension of the indication to “pre-procedure prevention of acute hereditary angioedema (HAE) episodes” at the dosages in the Marketing Authorisation.