SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetor 100 U/ml powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 500 U* of C1-inhibitor**
After reconstitution the product contains 500 U/5 ml which correspond to a concentration of 100 U/ml.

* 1 U of C1-inhibitor corresponds to the quantity of C1-inhibitor present in 1 ml of fresh, normal plasma.
** produced from human plasma.

The specific C1-inhibitor activity is at least 4.0 U/mg of protein.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection
White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetor is intended for use in cases of congenital C1-inhibitor deficiency in the acute treatment of angioedema.

4.2 Posology and method of administration

Cetor therapy should be initiated under supervision of a physician experienced in the care of patients with C1 inhibitor deficiency. If the patient is properly trained, Cetor can also be administered by self administration.

The dosage to be administered depends on the severity and nature of the attack.. The following dosages serve as a guideline:

Adults and children > 12 years
1000 U at the first sign of onset of an acute attack, and, if the patient has not responded adequately after 60 minutes, a second dose of 1000 U.

Considering the limited data on the efficacy and safety of C1 esterase inhibitors in children below 12 years of age, no dosage recommendation can be given. (See Section 5.1).

The presence of antibodies against C1-inhibitor can substantially reduce the half-life of Cetor. In such

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situations it is advisable to measure the recovery of C1-inhibitor (functional activity measurement) if there is a suspicion of lack of efficacy.

**Method of administration**
Cetor should be administered by direct intravenous injection. It is recommended that the product be infused slowly, at a rate of 1 ml per minute.

**4.3 Contra-indications**
Hypersensitivity to the active substance or to one or more of the excipients.

**4.4 Special warnings and precautions for use**
In the case of patients having antibodies against C1-inhibitor, account should be taken of the fact that an initially successful therapy can become less effective as the duration of the treatment increases. This expresses itself in the form of an increase in the seriousness and frequency of the angioedema attacks.

Cetor contains up to 24 mg sodium (approximately 1mmol) per dose of 2000 U solution, to be taken into consideration by patients on a controlled sodium diet.

In patients who displayed an atypical reaction during a previous use of blood or blood products, an anaphylactic reaction can occur. Such patients should preferably not be treated with the product, nor, similarly, with other blood products. If for some urgent reason this rule must be departed from, the preparation must be administered under close clinical control.

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 and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived C1-inhibitor product.

It is strongly recommended that every time that Cetor is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

There is limited experience with the use of Cetor in children and in the elderly; there is limited experience with Cetor in the treatment of AAE.

**4.5 Interaction with other medicinal products and other forms of interaction**
No interactions studies have been performed.
4.6 Pregnancy and lactation

**Pregnancy**
There are limited amount of data from the use of C1-inhibitor in pregnant women. Cetor is a physiological component of human plasma. Therefore no studies on reproduction and developmental toxicity have been performed in animals and no adverse effects on fertility, pre-and postnatal development are expected in humans.
Accordingly, Cetor should only be used during pregnancy where its use is indicated.

**Lactation**
It is unknown whether Cetor is excreted in human milk.
It should be considered whether to (dis)continue breast-feeding or to discontinue/abstain from Cetor therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and operate machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse reactions are based on post marketing experience as well as scientific literature. The standard categories of frequency are used:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>≥ 1/10</td>
</tr>
<tr>
<td>Common</td>
<td>≥ 1/100 and &lt; 1/10</td>
</tr>
<tr>
<td>Uncommon</td>
<td>≥ 1/1,000 and &lt; 1/100</td>
</tr>
<tr>
<td>Rare</td>
<td>≥ 1/10,000 and &lt; 1/1,000</td>
</tr>
<tr>
<td>Very rare</td>
<td>&lt; 1/10,000 (including reported single cases)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td>Rise in temperature, reactions at the injection site (e.g. rash)</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td>Allergic or anaphylactic-type reactions (e.g. tachycardia, hyper- or hypotension, flushing, hives, dyspnoe, headache, dizziness, nausea)</td>
</tr>
</tbody>
</table>

For safety with respect to transmissible agents, see 4.4.

4.9 Overdose

No symptoms of overdose with C1-inhibitor have been reported.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* anti-haemorrhagic, anti-fibrinolytic, proteinase inhibitors, C1-inhibitor;  
*ATC-code:* B02A B03

C1-inhibitor is a normal constituent of human blood and is one of the serine protease inhibitors ('serpins'). The protein functions as an inhibitor of the complement system and of the contact system (intrinsic clotting). The inhibition of the complement system results from the binding of C1-inhibitor to two of the active sub-units of the first component of the complement system (namely C1r and C1s). The contact system is inhibited by binding to factor XIIa and to kallikrein.

If C1-inhibitor is absent or its concentration reduced, or if the body's own C1-inhibitor is insufficiently active, this leads to a periodic symptomatology in which the occurrence of oedemas occupies a prominent place and which is denoted by the term hereditary angioedema. For the prophylaxis and the acute treatment of this symptomatology, a supplementary therapy with Cetor is used.

No clinical trials have been performed with Cetor in children. There are limited data on the efficacy and safety of C1 esterase inhibitors in children below 12 years of age. C1-inhibitor at 10 to 20 U/kg bodyweight or alternatively 500 U for bodyweight up to 50 kg and 1000 U for bodyweight 50 kg to 100 kg have been used without safety issue in the treatment of acute attacks in children with HAE.

Experience in the use of Cetor in pre-operative prophylaxis in cases of congenital C1-inhibitor deficiency is limited.

There is very limited experience in the use of Cetor and C1-inhibitor products in patients with Acquired Angioedema.

5.2 Pharmacokinetic properties

Absorption:  
Cetor is administered intravenously, there is no absorption phase. The bioavailability of Cetor administered to the patient will therefore be 100%.

Distribution:  
Following injection the in vivo recovery is 100%.  
The apparent volume of distribution is 3.1 L ± 0.1 L.

Elimination:  
Little is known about the mechanism of elimination in the body, but experimental data produce a monophasic falling curve, consistent with an open one-compartment model. The elimination half-life has been determined at 42 hours. The mean residence time (the time required for 62.3% of the administered dose of C1-inhibitor to be eliminated; comparable with the elimination half-life but calculated independently of the model used) is 65 hours. This applies equally to individuals with or without C1-inhibitor deficiency.  
The clearance in man is 0.053 L per hour.

The acute treatment and pre-operative prophylaxis of congenital and acquired angioedema with C1-inhibitor is replacement therapy. Therefore C1-inhibitor plasma levels are not only indicative for pharmacokinetics, but is also the primary pharmacodynamic parameter.
5.3 Preclinical safety data

C1-inhibitor is a normal constituent of the human body. In the case of animals, research into the level of toxicity is unreliable, given that at higher dosages overloading of the circulation occurs. Research into the toxicity for the embryo/foetus is not feasible due to the induction of, and disturbance by, antibodies. The preclinical studies on the safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development have not been conducted.

During the development of Cetor, research was carried out into the occurrence of a possible fall in blood pressure using a rat model, into the possible formation of neo-antigens (study in rabbits) and into the occurrence of thrombogenic effects (using a test described by Wessler) following administration of the product. No such undesirable effects were observed in the course of these studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: sodium chloride, saccharose, sodium citrate, L-Valine, L-Alanine, L-Threonine
Solvent: water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

From a microbiological point of view, the product should be used immediately. Chemical and physical in-use stability has been demonstrated for 3 hours at room temperature (15-25 °C).

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Cetor is 500 U of C1-inhibitor in a powder in a vial (glass Type I) with a stopper (bromobutyl) and a cap (aluminium).
The solvent is contained in a vial (glass Type I) with a stopper (bromobutyl) and a cap (aluminium).

6.6 Instructions for use, handling and disposal

Dissolution
The powder should be dissolved in the prescribed volume of solvent (5 ml). If stored at 2-8 °C it is necessary to bring the vials of Cetor and the water for injections to room temperature (15-25 °C) before dissolving the preparation.
Procedure using a transfer needle

1. Remove the plastic protective cap from both the vials containing the water for injections and the vial containing product.
2. Disinfect the rubber stoppers of both vials with a piece of gauze soaked in alcohol (70%).
3. Remove the protective cover from one end of the transfer needle and insert the needle into the vial containing the solvent. Then remove the protective cover from the other end of the transfer needle, turn the vial containing the transfer needle upside down and immediately insert the needle that is still free into the vial the powder.
4. The underpressure in the vial containing the powder will cause the solvent to be sucked into the vial. Recommendation: while the solvent is flowing across, the powder vial should be kept tilted and the water allowed to flow along the wall of the vial. This helps the product to dissolve more quickly. As soon as all the water has flowed across, the empty vial and the transfer needle should be removed in a single action.

In order to accelerate the dissolving process, the powder vial may be gently swirled around and, if necessary, heated to 30 °C. The vial should never be shaken nor should the temperature be allowed to exceed 37 °C.

If the vial is heated in a water bath, care should be taken to ensure that the water does not come into contact with the protective cap and/or the rubber stopper. As a rule, the dry matter should be fully dissolved within 10 minutes to form a clear (colourless to light blue) solution; the light blue colour is caused by the presence of the plasma protein ceruloplasmin.

Immediately before administration, the preparation should be visually inspected to see whether it contains any particulate matter or clots. If the preparation is not fully dissolved, or if the solution is not entirely clear or contains particulate matter, or if a clot has formed, the preparation should not be administered.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanquin
Plesmanlaan 125
1066CX Amsterdam

8. MARKETING AUTHORISATION NUMBER

Authorised in the Netherlands under RVG 19303.
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

25-11-2010