# C1 esterase inhibitor

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 11. Blood products, coagulation factors, and plasma substitutes > 11.2. Human immunoglobulins

EMLc | Codes ATC: En attente

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|---|---|
| **Indication** | Hereditary angioedema Code ICD11: 4A00.14 |
| **Type de médicament** | Biological agent |
| **Type de liste** | Liste complémentaire (EML) (EMLc) |
| **Formulations** | Parenteral > General injections > IV: 500 IU in vial powder for injection |
| **Historique des statuts LME** | Demande refusée en 2015 (TRS 994) |
| **Sexe** | Tous |
| **Âge** | Aussi recommandé pour les enfants |
| **Équivalence thérapeutique** | La recommandation concerne ce médicament spécifique |
| **Renseignements sur le brevet** | Lire la suite sur les brevets. |
| **Wikipédia** | C1 esterase inhibitor |
| **DrugBank** | C1 esterase inhibitor (Human C1-esterase inhibitor) |

## Résumé des preuves et recommandation du comité d'experts

An application was submitted by CSL Behring, Marburg, Germany, for the inclusion of human plasma-derived C1-esterase inhibitor (C1-INH) as a complementary medicine on the EML and EMLc for the acute treatment of recurrent episodes of subcutaneous and submucosal oedema in patients with types I and II hereditary angioedema (HAE). Reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to the application. Hereditary angioedema is a rare autosomal dominant genetic disorder, with estimated prevalence of approximately 1 in 50 000 persons; lower prevalence is reported in Asian populations (1, 2). Historically HAE was described as resulting from either deficiency (type I) or dysfunction (type II) of the plasma protein C1-inhibitor (C1-INH) (3). Plasma-derived C1-INH acts as replacement therapy in types I and II HAE. A third familial form of oedema has been identified in which patients have normal C1-INH levels and activity (type III HAE) (4). HAE is characterized by recurrent episodes of well-demarcated angioedema without urticaria, most often affecting the skin or the mucosal tissues of the upper respiratory and gastrointestinal tracts (5). In the absence of treatment, swelling generally resolves spontaneously in two to four days (6); however, laryngeal oedema (approximately 1% of all HAE attacks) may occur in up to 50% of patients and is potentially life-threatening (5, 7). Gastrointestinal attacks range from mild to severe, usually resolving without serious complications. Cutaneous attacks do not have serious complications; however, repeated episodes significantly disrupt patients' lives (8). Plasma-derived C1-INH is one of several medications available for acute treatment of episodes of angioedema in HAE. Others include icatibant, ecallantide and human plasma (either solvent/detergent-treated plasma or fresh frozen plasma, FFP). The application noted that, in regions where there is no access to plasma-derived C1-INH (or other newer treatments), the only treatment option for acute attacks in HAE patients is FFP. The Expert Committee noted that FFP is currently included on the EML and EMLc (9). However, clinical efficacy data for FFP in HAE are limited, and plasma contains substrates that could theoretically exacerbate symptoms (1, 10). Oral androgens have been used as long-term prophylaxis to reduce the frequency

and/or severity of attacks, but their side-effects (virilization, weight gain, menstrual irregularities) limit their use and they do not prevent life-threatening upper airway oedema with any certainty (4). The World Allergy Organization guidelines make a strong recommendation for treating HAE attacks in the general population with C1-INH, ecallantide or icatibant; for children, and for pregnant or lactating patients, the guidelines recommend plasma-derived C1-INH as the preferred, "on-demand" treatment for attacks (4). Treatment guidelines for hereditary angioedema are based on treatment initiated at the onset of acute attacks. Patients with laryngeal angioedema require immediate airway assessment because of the risk of fatal asphyxiation. Intubation may be needed in those with respiratory distress or stridor as even effective therapies take 30 minutes to begin working. The Committee noted that plasma-derived C1-INH can be self-administered, or given by a carer or nurse, through a peripheral intravenous line at the first sign of symptoms. The Expert Committee noted that the available evidence generally supported use of plasma-derived C1-INH as a safe and effective treatment for acute attacks of HAE. However, the clinical trials identified in the application were designed to investigate efficacy in a relatively limited situation, namely treatment for established attacks (11-14) Most trials measured time to relief of symptoms as the primary end-point. The Committee considered that these intermediate outcomes may not directly reflect "real life" where symptoms are treated early or at prodromal stages. No head-to-head trials comparing plasma-derived C1-INH with alternative treatments were presented. Plasma-derived C1-INH has wide regulatory approval in high-income countries, but registration in low- and middle-income countries is not as widespread. The application estimated treatment costs for a single acute attack ranging from US$ 1320–1980 in South America to US$ 3130–4695 in North America. The Expert Committee acknowledged the distressing effects of HAE on individual patients and their families but considered that the public health relevance of its treatment with C1-INH was unclear. In the absence of compelling evidence of a clinically relevant improvement in important treatment outcomes such as morbidity and mortality, the Expert Committee decided not to recommend the addition of plasma-derived C1-esterase inhibitor to the EML or EMLc. References: 1. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med. 2001;161(20):2417-29. 2. Bowen T, Cicardi M, Bork K, Zuraw B, Frank M, Ritchie B, et al. 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