C1 esterase inhibitor

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

EMLc | ATC codes: Pending

Indication	Hereditary angioedema ICD11 code: 4A00.14
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 500 IU in vial powder for injection
EML status history	Application rejected in 2015 (TRS 994)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	C1 esterase inhibitor
DrugBank	C1 esterase inhibitor (Human C1-esterase inhibitor)

Summary of evidence and Expert Committee recommendations

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. Hereditary angiodema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol. 2008;100(1 Suppl 2):S30-40. 3. Bork K, Davis-Lorton M. Overview of hereditary angioedema caused by C1-inhibitor deficiency: assessment and clinical management. Eur Ann Allergy Clin Immunol. 2013;45(1):7-16. 4. Craig T, Aygoren-Pursun E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO Guideline for the Management of Hereditary Angioedema. World Allergy Organ J. 2012;5(12):182-99. 5. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. Am J Med. 2006;119(3):267-74. 6. Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008;359(10):1027-36. 7. Bork K, Hardt J, Schicketanz KH, Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. Arch Intern Med. 2003;163(10):1229-35. 8. The selection and use of essential medicines. Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2014. (WHO Technical Report Series, No. 985). 9. Cicardi M, Zuraw B. Hereditary angioedema: Treatment of acute attacks. In: UpToDate [website]. Waltham, MA: UpToDate; 2014. 10. Bowen T, Cicardi M, Farkas H, Bork K, Longhurst HJ, Zuraw B, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy Asthma Clin Immunol. 2010;6(1):24. 11. Craig TJ, Levy RJ, Wasserman RL, Bewtra AK, Hurewitz D, Obtulowicz K, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol. 2009;124(4):801-8. 12. Craig TJ, Bewtra AK, Bahna SL, Hurewitz D, Schneider LC, Levy RJ, et al. C1 esterase inhibitor concentrate in 1085 hereditary angioedema attacks - final results of the I.M.P.A.C.T.2 study. Allergy. 2011;66(12):1604-11. 13. Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. N Engl J Med. 2010;363(6):513-22. 14. Riedl MA, Hurewitz DS, Levy R, Busse PJ, Fitts D, Kalfus I. Nanofiltered C1 esterase inhibitor (human) for the treatment of acute attacks of hereditary angioedema: an open-label trial. Ann Allergy Asthma Immunol. 2012;108(1):49-53.

