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Health Technology Briefing
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Human C1-esterase inhibitor (subcutaneous injection) for preventing hereditary angioedema

Company/Developer	CSL Behring UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 2773	NICE TSID: Not available	UKPS ID: Not available

Licensing and Market Availability Plans

This technology was licenced in the UK on 19th January 2018 for this indication.[1,2]

Summary

Human C1-esterase inhibitor (C1-INH) subcutaneous (SC) is licenced for the prevention of hereditary angioedema (HAE). HAE is a rare genetic disorder of blood vessels characterised by recurrent episodes of severe swelling (angioedema) below the skin which often affect the face, throat, stomach, hands or feet, causing discomfort and pain. People with HAE have reduced levels of a protein called C1-esterase inhibitor in their blood. C1-esterase inhibitor is a protein required to control the proteins in the blood that fight infections. HAE may be life threatening when the swelling occurs in the throat as it can obstruct the airways and impede breathing.

C1-INH is a medicinal form of the protein C1-esterase inhibitor that is extracted from human blood. The medical product treats the root cause of C1-esterase inhibitor deficiency by replacing missing or dysfunctional C1- esterase inhibitor which quickly increases C1- esterase inhibitor levels. C1-INH is administrated by SC (under the skin) injection. If commissioned into the UK, SC C1-INH will provide an alternative option for people with HAE who have trouble with the intravenous formulation.

Proposed Indication

Prevention of recurrent hereditary angioedema (HAE) attacks in adolescent and adult patients with C1-esterase inhibitor deficiency.[1,2]

Technology

Description

Human C1-esterase inhibitor (Berinert; C1-INH) is a plasma-derived medicinal form of the protein C1-esterase inhibitor. C1-esterase inhibitor regulates multiple pathways and normal production of bradykinin generation and decreases vascular permeability.[1,3] C1-INH treats the root cause of C1-esterase inhibitor deficiency with rapid uptake of C1-esterase inhibitor and replaces missing or dysfunctional C1-esterase inhibitor, which quickly increases C1-esterase inhibitor levels.[3] Under physiological conditions, C1-INH blocks the classical pathway of the complement system by inactivating the enzymatic active components C1s and C1r. In addition, it serves, besides alpha-2-macroglobulin, as the main inhibitor of plasma kallikrein. The therapeutic effect of C1-INH in HEA is induced by the substitution of the deficient C1-esterase inhibitor activity.[1]

C1-INH is indicated for prevention of recurrent HAE. It is intended for self-administration by subcutaneous (SC) injection which contains 2000 or 3000 IU per injection vial. The recommended dose of C1-INH for both adults and children is 60 IU/kg body weight twice weekly (every 3-4 days).[1,2]

Key Innovation

Routine prophylaxis with intravenous (IV) long-term C1-INH replacement therapy has been used since 2008. However, with IV C1-INH, patients may still experience attacks, and some patients may have venous access challenges. A highly concentrated human plasma-derived C1-INH for SC injection has been approved by regulatory agencies for long-term prevention of HAE attacks in adolescents and adults based on the phase III COMPACT (NCT01912456) study.[4] The currently approved SC C1-INH dose of 60 IU/kg of body weight administered subcutaneously twice weekly reduces the attack rate by a median of 95% and the use of rescue medications is reduced by a median of 100%.[5] If commissioned into the UK, SC human C1-INH will provide an alternative option for people with HAE who have trouble with the IV formulation.

Regulatory & Development Status

SC C1-INH currently has Marketing Authorisation in the EU/UK for prevention of recurrent HAE attacks in adolescents and adults with C1-esterase inhibitor deficiency. [1,2]

C1-INH was granted an orphan drug designation in the USA in October 1992 for prevention and/or treatment of acute attacks of HAE. [6]

Patient Group

Disease Area and Clinical Need

HAE is a rare hereditary disease caused by a deficiency or dysfunction of protein C1-esterase inhibitor.[7] HAE is a long-term and potentially life-threatening disease that can obstruct the airways and impede breathing during its attacks.[8,9] HAE symptoms include episodes of angioedema (swelling) in various parts of the body including the stomach, hands, feet, arms, legs, throat, and face.[7] Symptoms can start at any

time from early childhood.[9] The attacks of HAE can be triggered by trauma, pressure, emotional stress and the use of medications, especially inhibitors of angiotensin-converting enzyme (ACE) and oestrogens, which may induce and/or exacerbate quiescent disease in all types of HAE.[10] The most common form of HAE is HAE type I, which is the result of abnormally low levels of C1-esterase inhibitors (known as complements). They help to regulate various body functions (e.g., flow of body fluids in and out of cells). HAE type II, a more uncommon form of the disorder, occurs as the result of the production of abnormal complement proteins.[11]

The pain and disability caused by attacks may inhibit patients' ability to conduct their normal activities of daily life, including attending work or school. Also, unpredictable attacks make it difficult for patients to plan for travel or other life events. Patients may spend years without appropriate therapy and are at risk for a potentially life-threatening airway attack.[12] HAE UK estimate that HAE affects between 1/10,000 to 1/50,000 of the population.[9] Mutations can result in either low levels of C1INH (approx. 85% of cases) or normal levels of C1INH but with decreased function (approx. 15% of cases).[13] It is also estimated that one in 50,000 to 150,000 individuals is affected by this disorder worldwide.[11] At the time of writing this briefing, the population likely to be eligible to receive SC C1-INH could not be estimated from available published sources.

Recommended Treatment Options

While there is no cure for HAE, long-term preventive treatments are used routinely to reduce the need for treatment of acute attacks.[14] NICE currently recommends the following therapies for preventing recurrent attacks of hereditary angioedema in people aged 12 years and older:[15,16]

- Berotralstat
- Lanadelumab

Clinical Trial Information

Trial	NCT01912456; 2013-000916-10; A Double-blind, Randomised, Placebo-controlled, Cross-over Study to Evaluate the Clinical Efficacy and Safety of Subcutaneous Administration of Human Plasma-derived C1-esterase Inhibitor in the Prophylactic Treatment of Hereditary Angioedema **Phase III**- Completed **Location(s):** 5 countries in EU, UK, US, Canada, and other countries **Study completion date:** October 2015
Trial Design	Randomised, crossover assignment, quadruple-masked
Population	N=90 (actual) male or female over 12 years old with a clinical diagnosis of hereditary angioedema type I or II
Intervention(s)	C1-esterase inhibitor, SC, 40 or 60 IU/kg of body weight twice weekly for 16 weeks, preceded or followed by a placebo period[5]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: The Time-normalized Number of Hereditary Angioedema Attacks [Time Frame: During the treatment phase, up to 28 weeks.]

	See trial record for full list of other outcomes.
Results (efficacy)	See trial record.
Results (safety)	See trial record.

Estimated Cost

Cost of SC C1-INH was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Berotralstat for preventing recurrent attacks of hereditary angioedema (TA738). October 2021.
- NICE technology appraisal guidance. Lanadelumab for preventing recurrent attacks of hereditary angioedema (TA606). October 2019.

NHS England (Policy/Commissioning) Guidance

- NHS Clinical Commissioning Policy: Plasma derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II. 16045/P. July 2016.
- NHS Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angioedema (Adult). April 2013.

Other Guidance

- Marcus Maurer, Markus Magerl, Stephen Betschel et al. The international World Allergy Organisation (WAO)/European Association of Allergy & Immunology (EAACI) guideline for the management of hereditary angioedema—The 2021 revision and update. January 2022.[17]
- Paula J. Busse, Sandra C. Christiansen et al. US HAE Association Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. 2021.[18]
- Stephen Betschel, Jacquie Badiou2, Karen Binkley et al. The International/Canadian Hereditary Angioedema Guideline. 2019.[19]

Additional Information

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