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Health Technology Briefing
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Concizumab for treating haemophilia A and haemophilia B

Company/Developer	Novo Nordisk Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27612	NICE ID: 10414	UKPS ID: 655202

Licensing and Market Availability Plans

Currently in phase III/II clinical trials.

Summary

Concizumab is in development to prevent bleeding episodes in haemophilia A (HA) or haemophilia B (HB), with or without inhibitors. Haemophilia is an inherited disorder caused by lack of blood clotting factor which makes patients prone to excessive and uncontrolled bleeding. HA and HB are treated with replacement factor VIII (FVIII) and factor IX (FIX) to restore blood clotting and prevent bleeding. A major challenge to treatment of HA/HB is that patients can develop antibodies, called inhibitors, which make treatment less effective.

Concizumab is a monoclonal antibody (a type of protein) that has been designed to recognise, attach to and block a molecule in the body called 'tissue factor pathway inhibitor' (TFPI). TFPI controls another pathway for blood clotting that does not involve factor VIII or IX. By blocking TFPI, this medicine is expected to increase the ability of the blood to clot and help control the bleeding disorder, bypassing the need for replacement factor VIII or IX. Concizumab is a once daily injection given under the skin, which can be used at home and is easier to administer than replacement factor VIII or IX which have to be given directly into the vein.

Proposed Indication

HA and HB with or without inhibitors.[1,2]

Technology

Description

Concizumab (Anti-TFPI monoclonal antibody; mAb-2021; NN-7415; NNC-0172-0000-2021; NNC-0172-2021; NNC-172-2021)[3] is a humanized, monoclonal antibody which binds with high affinity to TFPI. TFPI is a potent inhibitor of the coagulation initiation phase, specifically the activation of FX to activated FX (Fxa) by the TF/FVIIa complex. Concizumab prevents downstream inhibition of FXa and FVIIa/TF by inhibiting the activity of TFPI allowing sufficient FXa to be produced. This ensures the restoration of thrombin generation and haemostasis in patients with HA and HB regardless of the presence of inhibitors.[4,5]

Concizumab is in clinical development for the prophylactic treatment of HA and HB with or without inhibitors. In the phase III clinical trials explorer7 (NCT04083781)[1] and explorer8 (NCT04082429)[2] participants receive a loading dose of 1.0mg/kg of concizumab via subcutaneous injection with a pen injector followed by an initial daily dose of 0.20 mg/kg concizumab from treatment day 2. Participants then receive daily, dose-adjusted concizumab (0.15-0.25mg/kg).

Key Innovation

Concizumab is a prophylactic treatment for HA and HB with and without inhibitors designed to be used as an alternative to prophylaxis with replacement FVIII or FIX. Concizumab meets the need for treatment options for the significant proportion of patients who develop inhibitors which render replacement FVIII or FIX less effective.[5] Current management strategies for patients with inhibitors include immune tolerance induction (ITI) or use of a bypassing therapy, however both strategies are costly and impact patient outcomes.[6,7]

Concizumab's novel mechanism of action means it will still be effective in HA and HB patients who have developed inhibitors to current standard-of-care factor replacement therapy. Currently there are no HA/HB therapies recommended by NICE that target the TFPI pathway.[4] Concizumab can be administered subcutaneously which is easier and less invasive compared to intravenous (IV) administration required for prophylactic FVIII or FIX replacement therapy and bypassing agents.[8,9]

Regulatory & Development Status

Concizumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Concizumab received orphan drug designation in the EU for HB (EU/3/17/1940) in January 2018.[10]

Concizumab is not currently in phase II or III development for any other indications.[11]

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Patient Group

Disease Area and Clinical Need

HA and HB are rare genetic bleeding disorders caused by mutations in the genes encoding FVIII and FIX respectively. HA and Ab are inherited via an X-linked recessive pattern, with males much more likely to be affected as they carry a single X chromosome. When FVIII or FIX are deficient or dysfunctional in HA/HB, the pathway of the coagulation cascade cannot be activated in the normal way, resulting in deficient thrombin generation and clot formation.[7,12] Patients with HA and HB are more prone to sudden and prolonged bleeding. The symptoms of hemophilia depend on its severity but can include nosebleeds; excessive wound bleeding; bleeding gums; and bruising. Recurrent bleeds lead to progressive joint damage and associated disability. Bleeds can be life-threatening if they occur in the brain or gastrointestinal system. HA and HB are life-long diseases, associated with significant psychological and social burden on patients and their families.[10] Some people who take blood clotting factor medicine develop antibodies in their immune system, called inhibitors, which make the medicine less effective.[13]

Hemophilia is a rare disorder, with an incidence ~1 in 10000 live births worldwide. HA is the most common form (>80% of the total hemophilia population) affecting 1 in 5,000 live male births, versus 1 in 30,000 live male births for HB.[12] In the UK, 8,740 people are living with HA, of which 2,140 have severe HA; and 1,946 people are living with HB, of which 370 have severe HB.[9] Approximately 7% of HA patients and 1% of HB patients in the UK have a historical or ongoing clinically relevant inhibitor.[9] In England, in 2020-21, there were 2,540 finished consultant episodes (FCE) and 2,411 admissions for hereditary FVIII deficiency and hereditary FIX deficiency (ICD-10 codes D66 and D67) which resulted in 2,010 day cases and 2,204 FCE bed days.[14]

Recommended Treatment Options

There is currently no cure for HA or HB. The condition requires on-demand treatment as an immediate response to bleeding episodes and regular injections of prophylaxis treatments to prevent bleeding episodes. Factor replacement therapy is the treatment of choice for people with haemophilia, which may be plasma-derived or recombinant.[15] Extended half-life (EHL) recombinant replacement factor are available which require less frequent administration (weekly); of these, octocog alfa (Kovaltry) and nonacog alfa (BENEfix) are EMA approved for treatment of HA and HB respectively, however only nonacog alfa is currently available in the UK.[16,17]

HA and HB patients who develop inhibitors can receive:

- ITI (daily or near daily replacement therapy, mean duration 12 months)
- Bypassing agent such as recombinant factor VIIa (rFVIIa, Novoseven) and factor VIII bypassing agent (FEIBA) (IV)[6]

Patients with severe HA or HA with inhibitors may be eligible to switch to emicizumab (subcutaneous injection, every 1-4 weeks).[9]

Clinical Trial Information	
Trial	NCT04082429, 2018-004891-36; **Efficacy and safety of concizumab prophylaxis in patients with haemophilia a or b without inhibitors (explorer8)** **Phase III** - Recruiting **Location(s):** 14 EU, UK, US, Canada and other countries **Primary completion date:** May, 2022
Trial Design	Randomised, parallel assignment, open label
Population	N=158; male; 12 years and older; congenital severe haemophilia A or B
Intervention(s)	Concizumab prophylaxis, administered daily (subcutaneous injection)
Comparator(s)	No comparator
Outcome(s)	• The number of treated spontaneous and traumatic bleeding episodes [Time Frame: From start of the new concizumab dosing regimen (week 0) up until the confirmatory analysis cut-off (at least 32 weeks) See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT04083781, 2018-004889-34; **Efficacy and safety of concizumab prophylaxis in patients with haemophilia a or b with inhibitors (explorer7)** **Phase III** - Active, not recruiting **Location(s):** 11 EU, UK, US, Canada and other countries **Primary completion date:** November 2021
Trial Design	Randomised, parallel assignment, open label
Population	N=136; male; 12 years and older; congenital HA or HB of any severity with documented history of inhibitor; patient has been prescribed, or in need of, treatment with bypassing agents in the last 24 weeks prior to screening (for patients not previously enrolled in explorer 4)
Intervention(s)	Concizumab prophylaxis, administered daily (subcutaneous injection)
Comparator(s)	No comparator
Outcome(s)	• The number of treated spontaneous and traumatic bleeding episodes [Time frame: from start of the new concizumab dosing regimen (week 0) up until the primary analysis cut-off (at least 32 weeks)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT03196284; 2016-000510-30; **A multi-centre, randomised, open-label, controlled trial evaluating the efficacy and safety of prophylactic administration of concizumab in haemophilia a and b patients with inhibitors (explorer4)** **Phase II** - Completed **Location(s):** 7 EU, UK, US, Canada and other countries **Primary completion date:** January, 2020
Trial Design	Randomised, parallel assignment, open label
Population	N=26; male; 18 years and older; haemophilia A or B patients with inhibitors
Intervention(s)	Concizumab prophylaxis, administered daily (subcutaneous injection)
Comparator(s)	Eptacog alfa and concizumab
Outcome(s)	• The number of bleeding episodes [Time frame: during at least 24 weeks from treatment onset (week 0)] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Clinical Trial Information	
Trial	NCT03196297, 2016-000614-29; **A multi-centre trial evaluating efficacy and safety of prophylactic administration of concizumab in patients with severe haemophilia a without inhibitors (explore5)** **Phase II** - Completed **Location(s):** 5 EU, UK, US and other countries **Primary completion date:** June 2020
Trial Design	Single group assignment, open label
Population	N=36; male; with severe haemophilia A
Intervention(s)	Concizumab prophylaxis, administered daily (subcutaneous injection)
Comparator(s)	No comparator
Outcome(s)	• The number of bleeding episodes during at least 24 weeks from treatment onset [time frame: during at least 24 weeks from treatment onset] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of concizumab is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Etranacogene dezaparvovec for treating haemophilia B (GID-TA10870). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Valoctocogene roxaparvovec for treating severe haemophilia A (GID-10682). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages). August 2019
- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages). 170067/P. July 2018
- NHS England. Clinical Commissioning Policy: Immune Tolerance Induction (ITI) for haemophilia A (all ages). 16042/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Haemophilia (all ages). B05/S/a

Other Guidance

- British Society for Haematology. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. 2020.[8]
- World Federation of Hemophilia Guidelines for the Management of Hemophilia, 3rd edition. 2020.[15]
- British Society for Haematology. Diagnosis and Treatment of Factor VIII and IX Inhibitors in Congenital Haemophilia. 2013.[7]
- A United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guideline approved by the British Committee for Standards in Haematology: guideline on the use of prophylactic factor VIII concentrate in children and adults with severe haemophilia A. 2010.[18]
- A United Kingdom Haemophilia Center Doctors' Organisation (UKHCDO) guideline approved by the British Committee for Standards in Haematology. Guideline on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders. 2008.[19]

Additional Information

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