Health Technology Briefing
June 2022

Benegrastim for treating chemotherapy-induced neutropenia in women with breast cancer

Company/Developer	Evive Biotech

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 24038	NICE ID: 11769	UKPS ID: Not Available

Licensing and Market Availability Plans

Completed phase III clinical development.

Summary

Benegrastim is being developed for the treatment of neutropenia in patients receiving chemotherapy treatment for breast cancer. Neutropenia occurs when an individual has low levels of neutrophils (a type of white blood cell), and it is a common side effect of cancer chemotherapy. Neutropenia can leave patients vulnerable to infections and cause complications such as febrile neutropenia (when neutropenia is accompanied by fever due to an infection) or neutropenic sepsis, which is potentially life-threatening. A common symptom of neutropenic sepsis is fever, and other signs include chills, fast heartbeat or breathing, cold or clammy skin, confusion, slurred speech, diarrhoea, and sickness. There are currently limited available treatments for chemotherapy-induced neutropenia and some of these require daily administration, which can be less convenient for patients.

Benegrastim is very similar to a human protein called granulocyte-colony-stimulating factor (G-CSF). It works by encouraging the bone marrow to produce more white blood cells, increasing white blood cell counts and so treating neutropenia and it has been shown to be effective in reducing the duration of severe neutropenia following chemotherapy treatment for breast cancer. Benegrastim only has to be administered once per chemotherapy cycle via subcutaneous (under the skin) injection with a fixed dose pre-filled syringe. If licenced, benegrastim will provide an additional option for the treatment of neutropenia in patients receiving chemotherapy for breast cancer.

Proposed Indication

Treatment of neutropenia in female patients receiving chemotherapy treatment for breast cancer.[1]

Technology

Description

Benegrastim (F-627, Ryzneuta) is a recombinant fusion protein containing human granulocyte-colony stimulating factor (G-CSF) and IgG2-Fc fragment. It is intended to reduce chemotherapy induced neutropenia by utilising the neutrophilic proliferating and activating properties of G-CSF.[2] Benegrastim elicits immunomodulating and haematopoietic activities by binding to the cell surface G-CSF receptors (G-CSFRs) and inducing receptor dimerization and activation of signalling cascades; this stimulates neutrophil progenitor proliferation and differentiation.[3]

Benegrastim is currently in clinical development for the treatment of neutropenia in female patients receiving chemotherapy for breast cancer. In the phase III trial, (NCT03252431), patients were administered benegrastim via a 20mg fixed dose pre-filled syringe on day two of each four chemotherapy cycles.[1]

Key Innovation

Benegrastim has been shown in clinical trials to have a comparable safety and efficacy profile to the current chemotherapy-induced neutropenia treatment pegfilgrastim and it is effective in reducing the duration of severe neutropenia following chemotherapy treatment for breast cancer.[2] If licenced, benegrastim will provide an additional option for the treatment of neutropenia in patients receiving chemotherapy for breast cancer.

Regulatory & Development Status

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

Benegrastim is in phase III clinical development for the prophylactic treatment of chemotherapy-induced neutropenia in women with breast cancer receiving myelotoxic chemotherapy.[4]

Patient Group

Disease Area and Clinical Need

Neutropenia is condition where you have a low number of white blood cells called neutrophils in your blood. When you have low levels of neutrophils in your blood, your immune system is weakened, making it harder for your body to fight infection.[5] The normal range for neutrophils is 2.5-7.5 x 10^9/L. Moderate neutropenia is defined as a neutrophil count of 0.5-1.0 x 10^9/L. Severe neutropenia is a count of <0.5 x 10^9/L.[6] Neutropenia is a risk factor for the development of infection and sepsis, especially in patients receiving high-intensity chemotherapy regimens.[7] Neutropenic sepsis is a potentially life-threatening complication of being neutropenic. A common symptom of neutropenic sepsis is fever (febrile neutropenia), and other signs include chills, fast heartbeat or breathing, cold or clammy skin, confusion, slurred speech, diarrhoea and sickness.[8]

Febrile neutropenia is observed in about 8 cases per 1000 people receiving cancer chemotherapy and the incidence of idiosyncratic drug-induced agranulocytosis or acute neutropenia is reported as 2.4-15.4 cases

per million.[9,10] In England (2020-21), there were 7,102 finished consultant episodes (FCE) and 5,567 admissions for agranulocytosis (ICD-10 code D70) which resulted in 18,732 FCE bed days and 1,069 day cases.[11]

Recommended Treatment Options

Recombinant human granulocyte-colony stimulating factors (rhG-CSFs) stimulate the production of neutrophils and may reduce the duration of chemotherapy-induced neutropenia and thereby reduce the incidence of associated febrile neutropenia. The National Institute for Health and Care Excellence (NICE) currently recommends the following G-CSFs for the treatment of neutropenia:[7]

- Filgrastim
- Lenograstim
- Lipegfilgrastim
- Pegfilgrastim

Clinical Trial Information

Trial	NCT03252431, 2016-003553-15; A Phase III, Randomized, Multi-Centre, Open-Label, Fixed Dose, Neulasta® Active-Controlled Clinical Trial of F-627 in Women With Breast Cancer Receiving Myelotoxic Chemotherapy **Phase III** – Completed **Location(s):** 3 EU countries and USA **Study completion date:** March 2020
Trial Design	Randomised, parallel assignment, double-blind
Population	N=393; Aged 18 years and older; Diagnosed with Stage I-III breast cancer; Subject is scheduled to undergo 4 cycles of neoadjuvant or adjuvant TC chemotherapy (docetaxel, cyclophosphamide, 75, 600 mg/m2, respectively)
Intervention(s)	Benegrastim 20mg subcutaneous (SC) injection
Comparator(s)	Pegfilgrastim (Neulasta) 6mg SC injection
Outcome(s)	Primary outcome: Duration in days of grade 4 neutropenia in chemotherapy cycle 1 [Time frame: the first of 4, 21-day chemotherapy cycles (average 3 weeks)] See trial record for full list of other outcomes
Results (efficacy)	See trial record
Results (safety)	See trial record

Estimated Cost

The cost of benegrastim is not yet known.

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Neutropenic sepsis: prevention and management in people with cancer (CG151). September 2012.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- BMJ Best Practice. Assessment of neutropenia. 2022.[12]
- European Society of Medical Oncology (ESMO). Management of febrile neutropenia: ESMO Clinical Practice Guidelines. 2016.[13]

Additional Information

Evive Biotech did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrials.gov. *Neulasta-controlled Trial of F-627 in Women With Breast Cancer Receiving Myelotoxic Chemotherapy*. *Trial ID: NCT03252431*. 2017. Available from: https://clinicaltrials.gov/ct2/show/NCT03252431 [Accessed 9 May 2022].

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13 Klastersky J, de Naurois J, Rolston K, Rapoport B, Maschmeyer G, Aapro M, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2016;27(suppl 5):v111-v8. Available from: https://doi.org/10.1093/annonc/mdw325.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.