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HEALTH TECHNOLOGY BRIEFING JANUARY 2021

Phelinun for reduced intensity conditioning treatment prior to allogeneic haematopoietic stem cell transplantation

NIHRIO ID	30262	**NICE ID**	10528
Developer/Company	Adienne Pharma & Biotech	**UKPS ID**	N/A

Licensing and market availability plans	Phelinun received a positive EMA CHMP opinion in September 2020.

SUMMARY

Phelinun is in development as a conditioning treatment prior to allogenic haematopoietic stem cell transplantation (HSCT) for various haematological diseases in children and adults. HSCT involves infusing stem cells from a donor into a patient whose bone marrow is damaged or defective. Conditioning treatment prior to HSCT is required in order to kill cancer cells, remove existing bone marrow from the patient and suppress the immune system, to reduce the risk of rejection from the transplant. Conditioning treatment is essential for a successful transplant but there are major associated side effects, including increased mortality. Therefore, there is a need for less toxic conditioning treatments.

Phelinun contains the active ingredient melphalan, which is already used to treat various cancers. It is also intended for the additional use of conditioning prior to HSCT. Phelinun is given by intravenous (IV) infusion and works by interfering in cellular processes, resulting in cell death. If licensed, phelinun will offer an additional treatment option for various cancers and conditioning prior to HSCT.

PROPOSED INDICATION

Phelinun indicated for the treatment of certain haematological and other cancers as well as conditioning treatment prior to haematopoietic stem cell transplantation (HSCT):[1,2]

- reduced intensity conditioning (RIC) treatment prior to allogeneic HSCT in malignant haematological diseases in adults
- RIC treatment in case of non-malignant haematological diseases in children
- myeloblative conditioning treatment in case of malignant haematological diseases in children

TECHNOLOGY

DESCRIPTION

Phelinun (melphalan hydrochloride) is a hybrid medicine. This means that it is similar to a reference medicine which contains the same active substance, but is intended for additional indications. The reference medicine for phelinun is alkeran 50mg/10ml, which, like phelinun, contains the active substance melphalan hydrochloride (melphalan).[1,3] Phelinun is intended for the additional use of conditioning treatment before patients undergo HSCT.[1]

Melphalan - which is the active substance of phelinun - is a bifunctional alkylating agent.[3] Melphalan is converted into highly reactive ethylenimmonium intermediates that induce covalent guanine N7-N7 intra and inter-crosslinks and alkylation of adenine N3 on DNA. This agent also alkylates RNA and protein structures. As a result RNA transcription and protein synthesis are inhibited, ultimately leading to cell growth arrest and/or death.[4]

Information regarding the treatment schedule could not be found, as no relevant trial for phelinun for the indication it is intended for could be identified. According to the EMA website phelinun will be available as 50mg and 200mg powder and solvent for concentrate for solution for intravenous (IV) infusion.[2,3]

INNOVATION AND/OR ADVANTAGES

Although the main studies to measure the effectiveness of phelinun for conditioning treatment in adults and children are not available, the company provided evidence from over 20 published studies to show that melphalan is effective for conditioning treatment in adults and children undergoing (blood) stem cell transplantation.[1] The benefits of phelinun from published studies in adults and children included increased overall survival; disease-free survival; event-free survival; non-relapse mortality and in some cases the side effects of phelinun may be lower than those of other options for conditioning treatment.[1,3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In September 2020, high-dose phelinun used alone or in combination with other cytotoxic medicinal products and/or total body irradiation received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for the treatment of:[2]

- multiple myeloma
- malignant lymphoma (Hodgkin, non-Hodgkin lymphoma)
- acute lymphoblastic and myeloblastic leukaemia
- acute myeloid leukaemia

- childhood neuroblastoma
- ovarian cancer
- mammary adenocarcinoma

In September 2020, phelinun in combination with other cytotoxic medicinal products received positive CHMP opinion as:[2]

- reduced intensity conditioning (RIC) treatment prior to allogeneic HSCT in malignant haematological diseases in adults
- RIC treatment in case of non-malignant haematological diseases in children
- myeloblative conditioning treatment in case of malignant haematological diseases in children

The most common side effects associated with phelinun (which may affect more than 1 in 10 people) include reduced levels of blood cells and platelets, infections, gastrointestinal disorders such as diarrhoea, vomiting, mouth ulcers and bleeding, and disorders of the immune system including graft-versus-host disease where transplanted cells attack the body.[1]

Phelinun is not currently in phase II or III development for any other indications.[5]

PATIENT GROUP

DISEASE BACKGROUND

The proposed new indication of phelinun in combination with other cytotoxic drugs, is for use in adults and the paediatric population; as conditioning treatment prior to allogeneic HSCT; for adults limited to malignant disease; for the paediatric population for both malignant and non-malignant conditions.[6]

HSCT is used to treat a wide spectrum of haematological and non-haematological disorders including lymphoma, leukaemia, immune-deficiency illnesses, congenital metabolic defects, haemoglobinopathies and myelodysplastic syndromes.[7,8] HSCT involves the IV infusion of stem cells to re-establish haematopoietic function in patients whose bone marrow or immune system is damaged or defective.[9] It is broadly divided up into autologous and allogeneic transplantation. Allogeneic HSCT is used to treat carefully selected patients with a range of malignant and non-malignant haematological disorders and other specific disorders of the immune system. It involves replacing the bone marrow stem cells of a patient with stem cells from a tissue-type matched or mismatched donor.[7]

CLINICAL NEED AND BURDEN OF DISEASE

In the United Kingdom (UK) and Republic of Ireland in 2018 there were 1675 allogeneic stem cell transplant procedures carried out amongst children and adults.[10]

Analysis from 15 uncontrolled studies reported five year survival following allogeneic HSCT to range from 62% to 90% with most studies reporting survival over 70%.[7]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Prior to HSCT, conditioning therapy is required to prepare the patient's bone marrow.[7,11] Conditioning treatments have a major impact on the success of the transplant. They are designed to reduce the risk of disease recurrence or rejection of the graft by the body.[11] The aim of conditioning is to kill leukaemia or tumour cells (in malignant diseases), eradicate existing bone marrow tissue in order to provide space for engraftment of transplanted donor stem cells and to suppress the patient's immune system to minimise the risk of graft rejection.[7]

Conditioning treatments have immediate major side effects such as increased mortality, graft-versus-host disease (with symptoms such as mouth blisters or skin rashes) and infections such as shingles or pneumonia. However, they are essential for a successful transplant. Conditioning treatment must ablate the bone marrow enough to remove remaining disease and allow the transplant to be accepted. However, it must not be so toxic that the patient dies of transplant-related causes such as infection.[11]

CURRENT TREATMENT OPTIONS

Current conditioning therapy involves chemotherapy with or without total body irradiation (TBI).[7]

Standard high-dose intensity (myoblative) conditioning regimens: [12]

- cyclophosphamide and TBI
- cyclophosphamide and busulfan
- cyclophosphamide and thiotepa
- high-dose busulfan with fludarabine with or without thiotepa
- treosulfan with fludarabine

RIC intensity condition regimens:[12]

- low-dose busulfan with fludarabine
- melphalan plus fludarabine

PLACE OF TECHNOLOGY

If licensed, phelinun will offer an additional treatment option for all indications that are currently treated by alkeran as well being used for conditioning treatment prior to HSCT.[1,2]

CLINICAL TRIAL INFORMATION

No relevant clinical trials were identified.

ESTIMATED COST

The estimated cost of phelinun is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Rivogenlecleucel for treating haematological cancers in children and young people undergoing haploidentical haematopoietic stem cell transplant (ID1601). Expected publication date to be confirmed.
- NICE technology appraisal in development. Rivogenlecleucel for treating haematological non-malignant diseases in children and young people undergoing haploidentical haematopoietic stem cell transplant (ID1496). Expected publication date to be confirmed.
- NICE technology appraisal. Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant (TA640). August 2020.
- NICE clinical guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE clinical guideline. Non-hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Guidelines for Leukaemia and other Myeloid Disorders – AML. 13-2H-106.
- Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised. B04/P/a.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Children). B04/S/b.
- NHS England. 2013/14 NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.
- NHS England. 2013/14 Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a
- NHS England. 2013/14 Standard Contract for Paediatric Oncology. E04/S/a
- NHS England. 2013/14 Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Society for Blood and Marrow Transplantation (EBMT). The EBMT Handbook: Haematopoietic Stem Cell Transplantation and Cellular Therapies. 2019.[13]
- A.Bazinet and G.Popradi. A general practitioners guide to hematopoietic stem cell transplantation. 2019.[14]

ADDITIONAL INFORMATION

Adienne Pharma and 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 European Medicines Agency (EMA). *Phelinun.* 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/phelinun [Accessed 03 December 2020].

2 European Medicines Agency (EMA). *Summary of opinion (initial authorisation): Phelinun.* 2020. Available from: https://www.ema.europa.eu/en/documents/smop/chmp-summary-positive-opinion-phelinun_en.pdf [Accessed 09 December 2020].

3 European Medicines Agency (EMA). *Phelinun Summary of Product Characteristics.* 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/phelinun-epar-product-information_en.pdf [Accessed 03 December 2020].

4 PubChem. *Melphalan hydrochloride.* 2006. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Melphalan-hydrochloride [Accessed 08 December 2020].

5 Clinicaltrials.gov. *Search for phelinun clinical studies: Phase II and III.* 2020. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=phelinun&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=[Accessed 09 December 2020].

6 European Medicines Agency (EMA). *Phelinun Assesment Report.* 2020. Available from: https://www.ema.europa.eu/en/documents/assessment-report/phelinun-epar-public-assessment-report_en.pdf [Accessed 09 December 2020].

7 NHS England. *Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages): Revised (B04/P/a).* Last Update Date: January 2015. Available from: https://www.england.nhs.uk/wp-content/uploads/2018/07/Haematopoietic-stem-cell-transplantation-All-Ages.pdf [Accessed 11 December 2020].

8 Hatzimichael, E., Tuthill M. *Hematopoietic stem cell transplantation.* Stem cells and cloning : advances and applications. 2010;3:105-17. Available from: https://doi.org/10.2147/SCCAA.S6815

9 Medscape. *Hematopoietic Stem Cell Transplantation.* 2018. Available from: https://emedicine.medscape.com/article/208954-overview#:~:text=Hematopoietic%20stem%20cell%20transplantation%20(HSCT)%20involves%20the%20intravenous%20infusion%20of,system%20is%20damaged%20or%20defective. [Accessed 11 December 2020].

10 British Society of Blood and Marrow Transplantation and Cellular Therapy (MSMBTCT). *2018 UK & ROI Transplant Table Indications.* 2018. Available from: https://bsbmtct.org/activity/2018/ [Accessed 04 January 2020].

11 National Institue for Health an Care Excellence (NICE). *Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant (TA640).* Last Update Date: 05 August 2020. Available from: https://www.nice.org.uk/guidance/ta640/resources/treosulfan-with-fludarabine-for-malignant-disease-before-allogeneic-stem-cell-transplant-pdf-82609131470533 [Accessed 11 December 2020].

12 National Institute for Health and Care Excellence (NICE). *Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant. Final Scope.* 2019. Available from: https://www.nice.org.uk/guidance/ta640/documents/final-scope [Accessed 11 December 2020].

13 European Society for Blood and Marrow Transplantation (EBMT). *The EBMT Handbook: Haematopoietic Stem Cell Transplantation and Cellular Therapies.* 2019. Available from: https://www.ebmt.org/sites/default/files/2019-01/2019_Book_TheEBMTHandbook.pdf [Accessed 04 January 2021].

14 Bazinet, A., Popradi G. *A general practitioner's guide to hematopoietic stem-cell transplantation.* Current oncology (Toronto, Ont). 2019;26(3):187-91. Available from: https://doi.org/10.3747/co.26.5033

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