Health Technology Briefing
December 2021

Eflornithine for treating neuroblastoma

Company/Developer	Norgine Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 5686	NICE ID: 10740	UKPS ID: 663073

Licensing and Market Availability Plans

Currently in phase II clinical trials

Summary

Eflornithine is in clinical development for the maintenance treatment of patients with high risk neuroblastoma. Neuroblastoma is a rare cancer which most often affects children under the age of 5 years but can also affect adults in rare instances. It develops in the nervous system from the uncontrolled growth of specialised nerve cells known as neuroblasts. Neuroblasts originate from foetal development. High risk neuroblastoma refers to a category of patients with neuroblastoma who have disease which has spread to sites beyond the initial tumour site and have too much expression of a gene known as MYCN, which can drive cancer growth. Patients are given maintenance treatment following full treatment or removal of the tumour, to try and stop the cancer coming back.

Eflornithine is a drug given as an oral tablet which blocks the action of an enzyme known as ornithine decarboxylase (ODC). ODC is involved in a process by which genes can promote uncontrolled tumour growth. Blocking ODC can therefore limit cancer cell growth. Despite the use of some treatments in the maintenance phase, patient's cancer often comes back and treatment outcomes beyond this point are limited. If licensed, eflornithine could offer a new maintenance treatment approach for patients with high risk neuroblastoma.

Proposed Indication

Maintenance treatment of children and adults aged up to 21 years with high risk neuroblastoma that is in remission[1,2]

Technology

Description

Eflornithine (Vaniqa, difluoromethylornithine, DFMO)[3,4] is an irreversible inhibitor of the ornithine decarboxylase (ODC) enzyme. The ODC1 gene is a direct target of the oncogene MYC, which is responsible for polyamine synthesis and can promote cell proliferation and oncogenic activity. Indirectly, inhibiting ODC can reduce polyamine synthesis, depleting tumours of polyamines and inhibiting the oncogenic activity of MYC.[5,6]

Eflornithine is currently in phase II clinical development for the maintenance treatment of children and adults aged up to 21 years with high risk.[1,2] neuroblastoma that is in remission. In the phase II clinical trial (NCT02395666), participants received 27 cycles of oral Eflornithine at a dose of 500 to 1000 mg/m^2 twice daily.[1]

Key Innovation

Despite the current treatments for neuroblastoma, disease often relapses and further treatment responses are limited. Maintenance treatment with eflornithine currently appears to improve survival and has manageable toxicities. Eflornithine targets a novel pathway and may provide a novel therapeutic strategy to maintain remission in patients with high-risk neuroblastoma.[7]

Regulatory & Development Status

Eflornithine topical cream has a Marketing Authorisation in the UK for the treatment of facial hirsutism in women.[4]

Eflornithine as a monotherapy and in addition to various other medicinal products is being developed for the following indications in phase II and III clinical trials:[8]

- Medulloblastoma
- Anaplastic astrocytoma (AA)
- Sun-damaged skin
- Familial adenomatous polyposis (FAP)
- Cervical cancer
- Prostate cancer
- Trypanosomiasis
- Colorectal cancer
- Barrett's oesophagus
- Skin cancer
- Gastric cancer
- Bladder cancer

Eflornithine received an EMA Orphan designation in September 2011 for the treatment of neuroblastoma.[9]

Patient Group

Disease Area and Clinical Need

Neuroblastoma is a cancer formed from a type of embryonic nerve cells known as neural crest cells. It arises in the sympathetic nervous system, which is located alongside the spinal cord from the neck through the chest and abdomen to the pelvis. Tumours often arise on the adrenal glands or in any nerve tissue along the sympathetic nervous system. Symptoms of neuroblastoma depend on the location of the tumour, but may include fatigue, fever and loss of appetite and an abdominal lump. High risk neuroblastoma refers to a prognosis in which patients are > 18 months of age, have metastatic disease and have MYCN oncogene amplification and overexpression.[10]

Neuroblastoma usually affects children under the age of 5 years. Approximately 90 children are diagnosed with neuroblastoma in the UK each year. Of these patients, 40% may be considered high-risk.[10] In England in 2020-21 there were 2,274 finished consultant episodes (FCE) and 2,139 hospital admissions for malignant neoplasm: medulla of adrenal gland (ICD-10 C74.1).[11] In 2017, the age-standardised incidence rate was 0.2 and 0.3 per 100,000 for males and females in England respectively.[12] High risk neuroblastoma is associated with a 5-year survival rate of approximately 30-50%.[10]

Recommended Treatment Options

The overall treatment pathway for patients with high-risk neuroblastoma is split in to three categories: induction, consolidation and maintenance. In the maintenance phase, the aim is to treat the patient for any minimal residual disease (MRD) following the induction and consolidation phases. Patients can be treated with an immunotherapy-based regimen if it is available as part of a clinical trial. Patients will also be treated with isotretinoin, with or without clinical trial involvement.[10]

Clinical Trial Information

Trial	**NMTT, NCT02679144, NMTRC014;** NMTT – Neuroblastoma Maintenance Therapy Trial Using Difluoromethylornithine (DFMO) **Phase II** – Recruiting **Locations:** USA, Canada **Primary Completion Date:** February 2024
Trial Design	Single group assignment, open-label
Population	N=258 (planned); children and adults aged 1 to 30 years with high risk neuroblastoma; in complete remission (CR)
Intervention(s)	Eflornithine (oral) – participants received eflornithine 750mg/m^2 ± 250mg/m^2 twice daily or 2500mg/m^2 twice daily for 730 days
Comparator(s)	-
Outcome(s)	Primary outcome measure: Number of participants with event free survival (EFS) during study [Time frame: 2 years] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**PEDS-PLAN, NCT02559778, NMTRC012;** A Study Using Molecular Guided Therapy With Induction Chemotherapy Followed by a Randomized Controlled Trial of Standard Immunotherapy With or Without DFMO Maintenance for Subjects With Newly Diagnosed High-Risk Neuroblastoma **Phase II** – Recruiting **Locations:** USA **Primary Completion Date:** September 2027
Trial Design	Randomized, parallel assignment, open-label
Population	N=500 (planned); children and adults aged up to 22 years with newly diagnosed high risk neuroblastoma
Intervention(s)	Eflornithine + ceritinib/dasatinib/sorafenib/vorinostat – participants received one of ceritinib/dasatinib/sorafenib/vorinostat, followed by standard immunotherapy with dinutuximab/GM-CSF/IL-2 and isotretinoin in addition to eflornithine 1000mg/m^2 twice daily for 730 days.
Comparator(s)	Ceritinib/dasatinib/sorafenib/vorinostat – participants received one of ceritinib/dasatinib/sorafenib/vorinostat, followed by standard immunotherapy with dinutuximab/GM-CSF/IL-2 and isotretinoin
Outcome(s)	Primary outcome measures: • Number of days from start of therapy to date of first relapse [Time frame: Up to 8 years] • Number of subjects that have a targeted agent chosen for treatment [Time frame: 2 years] • Number of subjects that receive 75% dosing of medications while on study protocol during cyles 3-6 [Time frame: 2 years] See trial record for a full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02395666, **NMTRC003B**; A Phase II Preventative Trial of DFMO (Eflornithine HCl) as a Single Agent in Patients With High Risk Neuroblastoma in Remission **Phase II** – Active, not recruiting **Locations:** USA **Primary Completion Date**: March 2018
Trial Design	Single group assignment, open-label
Population	N=140; children and adults aged up to 21 years with high risk neuroblastoma; in remission
Intervention(s)	Eflornithine (oral) – participants received 27 cycles at a dose of 500-1000mg/m^2 twice daily on each day of a 28 day cycle

Comparator(s)	-
Outcome(s)	Primary outcome measure: Number of participants with EFS during study [Time frame: 2 years] See trial record for a full list of other outcomes
Results (efficacy)	101 subjects enrolled on stratum 1 and 100 were eligible for ITT analysis; two-year EFS was 84% (±4%) and OS 97% (±2%). 39 subjects enrolled on stratum 2, with a two-year EFS of 54% (±8%) and OS 84% (±6%).[7]
Results (safety)	DFMO was well tolerated.[7]

Estimated Cost

The cost of eflornithine was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Dinutuximab beta for treating neuroblastoma (TA538). August 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Teenagers & Young Adults. B17/S/a.

Other Guidance

- National Cancer Institute. Neuroblastoma Treatment (PDQ) – Health Professional Version. 2021.[13]

Additional Information

References

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