Health Technology Briefing
March 2023

Eflornithine with lomustine for treating recurrent anaplastic astrocytoma

Company/Developer	Orbus Therapeutics Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 11521	NICE TSID: 10046	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

An anaplastic astrocytoma is a rare cancerous brain tumour that grows from astrocyte brain cells. Anaplastic means the cells divide rapidly and don't look like normal cells in structure or function. They affect adults and children and are often treated by neurosurgery followed by radiotherapy and sometimes chemotherapy. They're more common in adults between the ages of 30 and 70 and are more common in males. They are fast growing and often come back following treatment (known as a recurrence) in a more advanced form, so new treatment options are needed.

Eflornithine in combination with lomustine is currently in clinical development for the treatment of adult patients with recurrent anaplastic astrocytoma after irradiation and prior treatment with temozolomide chemotherapy. Eflornithine targets and inhibits a specific enzyme known as ornithine decarboxylase (ODC) and Lomustine is a supplementary treatment usually administered in combination with other chemotherapy. Studies show that inhibiting ODC activity reduces the growth of cancerous tumours. If licensed, eflornithine in combination with lomustine can offer a novel treatment option for patients with recurrent anaplastic astrocytoma that has progressed after irradiation and adjuvant (treatment given after irradiation) temozolomide chemotherapy.

Proposed Indication

Treatment of adult patients whose anaplastic astrocytoma has recurred/progressed after irradiation and adjuvant temozolomide chemotherapy.[1]

Technology

Description

Eflornithine (α-difluoromethylornithine) selectively targets and irreversibly inhibits ornithine decarboxylase (ODC), an enzyme essential for polyamine synthesis, and DNA and RNA function. ODC is an important enzyme that regulates cell division and is the first step of the synthesis of polyamines, converting ornithine to putrescine.[2] It is a novel cytostatic agent that irreversibly inhibits ornithine decarboxylase, a key enzyme in mammalian polyamine biosynthesis that is up-regulated in certain types of cancer.[3] Inhibition of ODC activity appears to revert the transformation of cells in vitro, reduces tumour growth in animal models and causes cell apoptosis in some tumors.[2] Lomustine is a supplementary treatment (usually administered in combination with other chemotherapy) with a mechanism of action that is believed to be partly as an alkylating agent and partly by inhibition of several steps in the synthesis of nucleic acid and inhibition of the repair of single strand breaks in DNA chains.[4]

Eflornithine is currently in clinical development in combination with lomustine for the treatment of recurrent anaplastic astrocytoma after irradiation and adjuvant temozolomide chemotherapy. In phase III clinical trial (NCT02796261), patients receive 2.8g/m^2 of eflornithine orally every 8 hours on a 2 weeks on 1 week off schedule, in combination with 90mg/m^2 of lomustine which given orally every 6 weeks.[1]

Key Innovation

ODC is an important enzyme that regulates cell division and is the first step of the synthesis of polyamines, converting ornithine to putrescine. Putrescine is a precursor for spermidine which, in turn, is a precursor for spermine. These chemicals are called polyamines. Cell studies have demonstrated that polyamines are important for stabilising DNA structure, the DNA double strand-break repair pathway, and as antioxidants. Further evidence points to putrescine being important to the function of RNA and transcription and underpins its importance as an essential enzyme for cell growth. In animal studies, eflornithine has been shown to inhibit the growth of malignant tumours, including intra cerebral mid- and high-grade gliomas. Eflornithine administration has also been shown to potentiate the anti-tumour activity of other chemotherapy agents.[2] If licensed, eflornithine will offer a novel treatment option for patients with recurrent anaplastic astrocytoma, when temozolomide chemotherapy has been ineffective, who currently have limited treatment options.

Regulatory & Development Status

Eflornithine topical cream currently has Marketing Authorisation in the EU/UK for the treatment of facial hirsutism in women.[5]

Lomustine currently has Marketing Authorization in the EU/UK as the following:[4]

- Palliative or supplementary treatment, usually in combination with radiotherapy and/or surgery as part of multiple drug regimens in:
  - Brain tumours (primary or metastatic)
  - Lung tumours (especially oat-cell carcinoma)
- Treatment of Hodgkin's disease (resistant to conventional combination chemotherapy)
  - Malignant melanoma (metastatic)
- Second-line treatment in non-Hodgkin's lymphoma, myelomatosis, gastrointestinal tumours, carcinoma of the kidney, the testis, the ovary, the cervix uteri and the breast

Eflornithine received the following regulatory designations:[6,7]

- EMA Orphan designation in June 2016 for the treatment of glioma
- US FDA Breakthrough therapy designation in 2014 for treatment of anaplastic glioma

Eflornithine is also in phase II/III clinical trials for the following indications:[8]

- Familial adenomatous polyposis
- Colorectal neoplasms
- Gastric cancer
- Prostate cancer
- Neuroblastoma
- Sun-damaged skin

Patient Group

Disease Area and Clinical Need

Anaplastic astrocytoma is a rare malignant brain tumour. Astrocytoma's are tumours that develop from certain star-shaped brain cells called astrocytes. Astrocytes and similar cells form tissue that surrounds and protects other nerve cells found within the brain and spinal cord. Collectively, these cells are known as glial cells and the tissue they form is known as glial tissue. Tumours that arise from glial tissue, including astrocytoma's, are collectively referred to as gliomas. The symptoms of anaplastic astrocytoma's vary depending upon the specific location and size of the tumour. The specific cause of this tumour is unknown. Astrocytoma's are classified according to a grading system developed by the World Health Organization (WHO). Astrocytoma's come in four grades based upon how fast the cells are reproducing and the likelihood that they will spread (infiltrate) nearby tissue.[9] Astrocytomas can be low grade (slow growing) or high grade (fast growing).[10] Grades III and IV astrocytoma's are malignant and may be referred to as high-grade astrocytoma's. Anaplastic astrocytoma's are grade III astrocytoma's.[9,11]

The exact incidence of these tumours is unknown. Anaplastic astrocytoma and glioblastoma multiforme are estimated to affect 5-8 people per 100,000 in the general population. Anaplastic astrocytoma's are more common in adults than children.[9] The 1 and 5 year relative survival rates of anaplastic astrocytoma's are 64.9% and 29.8%, respectively.[11] In adults, anaplastic astrocytoma's usually develop between 30 and 50 years of age.[12] In England (2021-22), there were 21,468 finished consultant episodes (FCE) and 16,418 admissions for malignant neoplasm of the brain (ICD-10 code C71), resulting in 76,631 FCE bed days and

7,931 day cases.[13] Astrocytomas are the most common type of brain tumours, accounting for around 34 out of every 100 brain tumour (34%) diagnoses.[10]

Recommended Treatment Options

NICE currently recommends the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) in children and adults over 3 years of age. For a patient whose tumour recurs or progresses following surgery/radiotherapy, the chemotherapy treatment options are limited because the currently available agents have only a small chance of being effective. Although high dose oral procarbazine is used as a single agent in the USA, it is not usual in the UK except in combination with lomustine and vincristine (PCV) regimen. This currently constitutes standard first line chemotherapy. Lomustine alone is sometimes used as first line therapy. The likelihood of response depends on age, tumour type and Karnofsky performance status.[14]

Clinical Trial Information

Trial	**STELLAR**; NCT02796261; A Randomized Phase 3 Open-Label Study To Evaluate the Efficacy and Safety of Eflornithine With Lomustine Compared to Lomustine Alone in Patients With AA That Progress/Recur After Irradiation and Adjuvant Temozolomide Chemotherapy **Phase III** - Active, not recruiting **Location(s):** Five EU countries, UK, USA, Canada, and other countries **Primary completion date:** June 2023
Trial Design	Randomised, parallel assignment, open label, active comparator controlled
Population	N=343; patients with anaplastic astrocytoma that has recurred/ progressed after radiation and adjuvant temozolomide chemotherapy; aged 18 years and older
Intervention(s)	Eflornithine (2.8 g/m^2 administered orally every 8 hours) dosed on a 2 weeks on, 1 week off schedule; Lomustine (90 mg/m^2 administered orally) dosed every 6 weeks.
Comparator(s)	Lomustine (110 mg/m^2 administered orally) dosed every 6 weeks.
Outcome(s)	Primary outcome: - Overall survival [time frame: 4 years] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated NHS indicative price of eflornithine topical cream is £56.87.[15] The estimated NHS indicative price of lomustine 40mg capsules is £780.82.[16]

Relevant Guidance

NICE Guidance
• NICE technology appraisal. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23). March 2016. • NICE guideline. Brain tumours (primary) and brain metastases in over 16s (NG99). January 2021.
NHS England (Policy/Commissioning) Guidance
• NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a. • NHS England. 2013/2014 NHS Standard Contract for Cancer: Brain/Central Nervous System (Adult). B13/S/a. • NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
Other Guidance
• European Association of Neuro-Oncology (EANO). EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. 2021.[17] • The Spanish Society of Medical Oncology (SEOM). SEOM clinical guidelines for anaplastic gliomas. 2017. [18]

Additional Information

Orbus Therapeutics, Inc 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

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