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Newcastle University

Health Technology Briefing
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Cabozantinib for previously treated locally advanced, unresectable or metastatic neuroendocrine tumours

Company/Developer	Ipsen Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 23778	NICE ID: Not applicable	UKPS ID: 674885

Licensing and Market Availability Plans

Currently in Phase III trials.

Summary

Cabozantinib is currently in clinical development for treating locally advanced, unresectable or metastatic neuroendocrine tumours. A neuroendocrine tumour (NET) is a rare cancerous tumour that can develop in many different organs of the body. It affects the cells that release hormones into the bloodstream. There are several different types of NETs and the type a person has depends on the type of cell the cancer started in. Most NETs develop slowly over some years and may not cause symptoms in the early stages. The symptoms of a neuroendocrine tumour depend on where in the body it is and what hormones it produces. For example, a tumour in the digestive system may cause diarrhoea, constipation or tummy pains. Currently, there are few treatment options for patients with NETs that have spread around the body or cannot be operated on, leaving an unmet need for additional treatment options.

Cabozantinib is a medicine taken by mouth that blocks the activity of enzymes known as tyrosine kinases. These enzymes can be found in certain receptors in cancer cells, where they are involved in cell division and the growth of new blood vessels to supply the cancer. By blocking the activity of these enzymes in cancer cells, the medicine reduces the growth and spread of the cancer. If licensed, cabozantinib may provide an additional treatment option for adults with NETs that have spread around the body or cannot be operated on.

Proposed Indication

Treatment of adult patients with advanced pancreatic or extra-pancreatic neuroendocrine tumours who have experienced progression after previous systemic therapy.[1]

Technology

Description

Cabozantinib (XL-184, Cabometyx) is a tyrosine kinase inhibitor (TKI) that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer.[2,3] Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of hepatocyte growth factor receptor protein (MET) and vascular endothelial growth factor (VEGF) receptors.[3] In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.[3] By blocking the activity of these enzymes in cancer cells, cabozantinib reduces the growth and spread of the cancer.[2]

Cabozantinib is currently in phase III clinical development for treating adult patients with locally advanced, unresectable or metastatic neuroendocrine tumours (NETs) of pancreatic and non-pancreatic origin whose disease has progressed after prior therapy.[1,4] In a placebo-controlled phase III trial (NCT03375320, CABINET) cabozantinib is administered orally in a dose of 60 mg once daily for 28 days, with cycles repeating every 28 days in the absence of disease progression or unacceptable toxicity.[1,5]

Key Innovation

There are currently few recommended treatments for adults with locally advanced or metastatic NETs.[6,7] It is recognised that there remains a critical need for new and effective therapies for patients with advanced neuroendocrine tumors.[8] While diagnostic advancements have enhanced NET detection, managing these tumours remains challenging. Numerous studies have sought to identify driver mutations and overexpression patterns in NETs, highlighting frequent mutations or overexpression of proteins involved in RTKs.[9] Specifically, VEGF has been recognised as a key oncogenic pathway in NETs.[10] Cabozantinib is a RTK inhibitor that targets VEGF receptor 2 amongst other RTKs.[10]

Cabozantinib has shown encouraging activity in NETs, both in vitro and in vivo models.[11] Therefore, if licensed, cabozantinib will offer an additional treatment for patients with locally advanced, unresectable or metastatic NETs.[8]

Regulatory & Development Status

Cabozantinib currently has Marketing Authorisation in the EU/UK for:[2,3]

- advanced renal cell carcinoma;
- hepatocellular carcinoma, for adults previously treated with sorafenib; and
- adults with locally advanced or metastatic differentiated thyroid carcinoma.

Cabozantinib is currently in phase II and III development for the treatment of:[12]

- solid tumours
- released and refractory myeloma
- kidney cancer
- cholangiocarcinoma
- glioblastoma
- colorectal cancer
- gastric and gastroesophageal carcinoma

- non-small cell lung cancer
- prostate cancer
- head and neck cancer
- breast cancer
- pancreatic cancer
- urothelial carcinoma
- cutaneous melanoma
- soft tissue carcinoma

Patient Group

Disease Area and Clinical Need

A NET is a rare tumour that can develop in many different organs of the body.[13] It affects the cells that release hormones into the bloodstream (neuroendocrine cells).[13] All NETs are malignant (a cancer) by definition.[14] There are a number of different types of NETs and the type depends on the type of cell that the cancer started in.[14] Around 50% of NETs start in the digestive system (including the stomach, small and large bowel, pancreas and rectum), while around 20% of NETs start in the lung.[14] NETs can also start in other places, such as the oesophagus, appendix, skin, prostate, womb, adrenal, parathyroid and pituitary glands.[14] Most NETs develop slowly over some years and may not cause symptoms in the early stages.[14] It is not unusual for people to find that a NET has already spread to another part of the body when they are diagnosed; when this happens, the NETs are metastatic.[14,15] When the cancer has grown outside the body part it started in but has not yet spread to other parts of the body, this is known as locally advanced.[15] Unresectable cancer is cancer that cannot be treated with surgery.[16] The symptoms of a NET depend on where in the body it is and what hormones it produces.[13] For example, a tumour in the digestive system may cause diarrhoea, constipation or tummy pains.[13] Some tumours may lead to abnormally large amounts of hormones being released into the bloodstream;[13] these are known as "functioning tumours" and can cause symptoms such as diarrhoea, flushing, cramps, wheezing, low blood sugar (hypoglycaemia), changes in blood pressure, and heart problems.[13] The cause of NETs is not fully understood.[13] However, people with one of the following inherited conditions have an increased chance of developing a tumour: multiple endocrine neoplasia type 1 (MEN1); neurofibromatosis type 1; and Von Hippel-Lindau syndrome (VHL).[13]

Over 4,000 people are diagnosed with a NET each year in the UK.[14] NETs can develop at any age, including in children, but the average age of diagnosis is around 50 to 60 years old.[14] In England (2022-23) there were 11,975 finished consultant episodes (FCEs) and 11,337 admissions for malignant neoplasms of thyroid and other endocrine glands (ICD-10 codes C73-C75), which resulted in 4,490 day cases and 24,005 FCE bed days.[17] More than 70% of people in the UK with a large bowel NET survive for one year or more, while around 80% with a rectal NET survive for one year or more.[18] Around 75 out of 100 people with all types of stomach NETs in the UK survive for 1 year after their diagnosis.[19]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommended everolimus and sunitinib for treating unresectable or metastatic NETs of pancreatic origin in adults, or unresectable or metastatic NETs of gastrointestinal or lung origin in adults with progressive disease. Additionally, NICE recommend lutetium (177Lu) oxodotreotide for treating adults with unresectable or metastatic somatostatin receptor-positive gastroenteropancreatic NETs.[6,7]

Clinical Trial Information

Trial	**CABINET,** NCT03375320; Randomized, Double-Blinded Phase III Study of CABozantinib Versus Placebo IN Patients With Advanced Neuroendocrine Tumors After Progression on Prior Therapy (CABINET) **Phase III** – Active, not recruiting **Location:** USA **Primary completion date (estimated)** – August 2023
Trial Design	Randomised, parallel-assignment, double-blind, placebo-controlled
Population	N=296 (actual); adults aged 18 years or older with locally advanced/unresectable or metastatic neuroendocrine tumours of pancreatic and non-pancreatic origin whose disease has progressed after prior therapy.
Intervention(s)	Oral cabozantinib S-malate, 60 mg once daily[5]
Comparator(s)	Placebo
Outcome(s)	Primary outcome: Progression-free survival (PFS) [Time frame: from randomisation to the first radiographic documentation of disease progression, or death from any cause, assessed for up to 8 years] See trial record for full list of other outcomes.
Results (efficacy)	Efficacy analyses in both the extra-pancreatic NET (epNET) and pancreatic (pNET) cohorts noted significantly improved PFS for patients receiving cabozantinib versus placebo.[5]
Results (safety)	No new safety signals were noted.[5]

Estimated Cost

The NHS indicative cost of 30 cabozantinib 60 mg tablets is £5,143.[20]

Relevant Guidance

NICE Guidance

- NICE Technology Appraisal awaiting development. Lutetium oxodotreotide with octreotide for newly diagnosed unresectable or metastatic gastroenteropancreatic neuroendocrine tumours [GID-TA11366]. Publication date TBC.
- NICE Technology Appraisal in development. Selective internal radiation therapy (SIRT) for neuroendocrine tumours metastatic to the liver [GID-IPG10336]. Published May 2024.
- NICE Technology Appraisal Guidance. Lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours (TA539). August 2018.
- NICE Technology Appraisal Guidance. Everolimus and sunitinib for treating unresectable or metastatic neuroendocrine tumours in people with progressive disease (TA449). June 2017.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

- NHS England. 2013/14 NHS Standard Contract for Specialised Endocrinology Services (Adult). A03/S/a.

Other Guidance

- Kos-Kudla et al. European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours. 2023.[21]
- Kaltsas et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for appendiceal neuroendocrine tumours (aNET). 2023.[22]
- Hofland et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. 2023.[23]
- Rinke et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for colorectal neuroendocrine tumours. 2023.[24]
- Sorbye et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for digestive neuroendocrine carcinoma. 2023.[25]
- Shah et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. 2021.[26]
- ESMO Guideline Committee. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2020.[27]
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Additional Information

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