NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Avapritinib for treating platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation-positive gastrointestinal stromal tumours

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of avapritinib within its marketing authorisation for platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation-positive gastrointestinal stromal tumours (GIST).

Background

Gastrointestinal stromal tumours (GIST) are a rare type of soft tissue sarcoma, (a rare cancer of mesenchymal origin), which develops in the digestive tract (most frequently in the stomach and small intestine but can arise anywhere along the gastrointestinal tract). The cancer cells associated with GIST are mainly found with an activating mutation in the tyrosine-protein kinase KIT, CD117 (KIT) gene but in a small number of cases the mutation occur in the platelet derived growth factor receptor alpha (PDGFRA) gene. Wild-type GIST is caused by no specific mutation types. Most GIST have changes in either the KIT or the PDGFRA gene exclusively. GIST with these mutations are considered aggressive and can spread quickly to other parts of the body and are not easily removed surgically.

GIST represents around 0.1 to 3% of all gastrointestinal cancers and the estimated incidence of GIST is around 15 cases per million corresponding to around 840 new cases per year in England. The proportion of patients with metastatic/unresectable GIST is between 10% and 30%.[1] People with the KIT mutation represent around 75-80%[2] of all GIST mutations and people with the PDGFRA mutation represent around 8 to 10% of all GIST mutations. Two-thirds will have the D842V-specific mutation which does not respond to existing pharmacological treatment. For around 8 to 10% of people with wild-type mutations, treatment options are variable with no standard of care.[3]

Treatment will depend where the tumour is located in the gastrointestinal tract and the risk of recurrence. Surgery is usually the first treatment used for GIST, however targeted drugs known as tyrosine kinase inhibitors can be used to treat tumours that are too large to be removed safely, or those that have already spread to other parts of the body.

NICE technology appraisal guidance 86 recommends imatinib as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST. This guidance notes that approximately 16% of patients will experience primary resistance to imatinib, and most patients will develop a reduced response at a later stage. However, NICE

technology appraisal guidance 209 does not recommend imatinib at an increased dose for people with unresectable and/or metastatic GIST whose disease has got worse after treatment with imatinib at the standard dose of 400 mg a day. NICE technology appraisal guidance 179 recommends sunitinib as a treatment option for people with unresectable and/or metastatic GIST whose treatment with imatinib has failed due to resistance or intolerance and NICE technology appraisal guidance 488 recommends regorafenib as a treatment option for people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, but only if their Eastern Cooperative Oncology Group (ECOG) performance status is 0 to 1.

The PDGFRA gene mutation may make the tumour resistant to current therapies to treat GIST. In England there are there are currently no approved therapies specifically for PDGFRA D842V-mutation GIST.

The technology

Avapritinib (Brand name unknown; Blueprint Medicines) is a tyrosine kinase inhibitor administered orally as tablets. It selectively inhibits activity of the KIT and PDGFRA genes. Avapritinib does not currently have a marketing authorisation in the UK. It has been studied in clinical trials for the treatment of adults with unresectable GIST with at least 3 prior lines of therapy and in adults with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior lines of therapy. It has also been studied in adults with locally advanced unresectable or metastatic GIST previously treated with imatinib and 1 or 2 other tyrosine kinase inhibitors.

Intervention(s)	Avapritinib
Population	• Adults with unresectable or metastatic GIST and the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation regardless of prior therapy

Comparators	• Imatinib (for adults who have KIT (CD117)-positive tumours) • Sunitinib (for adults whose treatment with imatinib has failed due to resistance or intolerance) • Regorafenib (for adults whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib) • Established clinical management without avapritinib including best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • response rate (including partial response rate and duration of response) • progression free survival • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of avapritinib is conditional on the presence of the PDGFRA D842V mutation. The economic modelling should include the costs associated with diagnostic testing for the PDGFRA D842V mutation in people with unresectable or metastatic GIST who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.

Other considerations	If the evidence allows the following subgroups will be considered. These include: • previous treatment with tyrosine kinase inhibitors • resistance or intolerance to tyrosine kinase inhibitors The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours (2017) NICE technology appraisal guidance 488. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (2014) NICE technology appraisal guidance 326 last reviewed April 2018. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (2010) NICE technology appraisal guidance 209. Sunitinib for the treatment of gastrointestinal stromal tumours (2009) NICE technology appraisal guidance 179 last reviewed July 2017. Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (2004) NICE technology appraisal guidance 86. **Related NICE Pathways:** Gastrointestinal cancers https://pathways.nice.org.uk/pathways/gastrointestinal-cancers
Related National Policy	**NHS England:** NHS England (2019) The NHS long term plan

	NHS England (2018) Manual for prescribed specialised services 2018/19 Chapter 105: specialist cancer services (adults). NHS England (2016) Robotic assisted surgery for oesophago-gastric cancers. Clinical Commissioning Policy. Reference: 16006/P. NHS England (2013) Oesophageal and Gastric (adult). 2013/14 NHS Standard Contract for Cancer. Reference: B11/S/a. NHS England (2013) 2013/14 NHS Standard Contract for Cancer: Chemotherapy (adult). 2013/14 NHS Standard Contract for Cancer. Reference: B15/S/a. NHS England (2018/2019) Chapter 105 specialist cancer services (adults) NHS manual for prescribed specialist services (2018/2019) **Department of Health:** Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance

References

[1] Patient UK (2014) Gastrointestinal Stromal Tumours. Accessed February 2020

[2] Starczewska Amelio J M, Ruzafa JC, Desai K et al (2014) Prevalence of gastrointestinal stromal tumour (GIST) in the United Kingdom at different therapeutic lines: an epidemiologic model. BMC Cancer 14:364 /doi.org/10.1186/1471-2407-14-364

[3] https://liferaftgroup.org/mutations-and-mutation-testing/. Accessed February 2020