NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Avapritinib for treating unresectable or metastatic gastrointestinal stromal tumours

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of avapritinib within its marketing authorisation for unresectable or metastatic 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 KIT gene but in a small number of cases the mutation occur in the PDGFRA gene or wild type GIST which 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 approximately 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%[3] of all GIST mutations of which two-thirds will have the D842V-specific mutation[3] which does not respond to existing pharmacological treatment. Around 8-10% of people with GIST have no specified (wild-type) mutations and treatment options are variable.[3]

Treatment will depend on what part of the GI tract the tumour is in and the risk category of recurrence. Surgery is usually the first treatment method used for GIST, however targeted drugs known as growth (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. There are several pharmacological options for unresectable or metastatic GIST.

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 400mg 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 (third-line) 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.

There are currently no lines of pharmacological therapy recommended specifically for the treatment of patients with unresectable or metastatic GIST when resistance to current therapies develops or whose disease has progressed upon treatment with third line therapy. The PDGFRA gene mutation may make the tumour resistant to the standard drugs to treat GIST and in England there are there are currently no approved therapies specifically for PDGRFA D842V-driven GIST.

The technology

Avapritinib (Brand name unknown; Blueprint Medicines) is a 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 patients with unresectable GIST with at least 3 prior lines of therapy and in patients with unresectable or metastatic GIST with the PDGFRA D842V mutation regardless of prior lines of therapy.

Intervention(s)	Avapritinib
Population	• Adults with unresectable or metastatic gastrointestinal stromal tumours (GIST) who have received at least 3 prior lines of therapy • Adults with unresectable or metastatic GIST and the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation regardless of prior therapy

Comparators	For adults with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy • Established clinical management without avapritinib including best supportive care For adults with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation regardless of prior therapy • 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 use of avapritinib is conditional on the presence of KIT or PDGFRA D842V mutations. The economic modelling should include the costs associated with diagnostic testing for the KIT or 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	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. Review date 2020 (month not known). 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 last reviewed October 2013 (currently assessed as up-to-date). Sunitinib for the treatment of gastrointestinal stromal tumours (2009) NICE technology appraisal guidance 179 last reviewed July 2017 (currently assessed as up-to-date). Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (2004) NICE technology appraisal guidance 86. **Appraisals in development (including suspended appraisals):** Gastrointestinal stromal tumours (unresectable, metastatic) - masitinib (after progression with imatinib) ID622. NICE technology appraisal guidance. Expected publication date to be confirmed. Suspended. **Appraisals in development (including suspended appraisals)** Gastrointestinal stromal tumours (unresectable, metastatic) - masitinib (after progression with imatinib) ID622. NICE technology appraisal guidance. Expected publication date to be confirmed. This was suspended in 2014 because the CHMP decided not to approve masitinib for treating

	unresectable or metastatic GIST after treatment with imatinib. **Related NICE Pathways:** Gastrointestinal cancers https://pathways.nice.org.uk/pathways/gastrointestinal-cancers **Related Quality Standards:** End of life care for adults (2011) NICE quality standard 13 last reviewed 2017
Related National Policy	**NHS England:** NHS England (2019) The NHS long term plan NHS England (2018) Highly specialised services 2017 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

Questions for consultation

Please describe what is considered to be 'established clinical management' at this time in the NHS for treating gastrointestinal stromal tumours:

- with the KIT-positive mutation
- with the PDGFRA-D842V mutation; and
- with wild type (no other specified) mutations.

Is mutational testing routinely conducted in the NHS for KIT-positive GIST? Is the PDGFRA-D842V mutation in GIST routinely tested for in the NHS?

Do people with PDGFRA-D842V GIST routinely receive the same treatment as people with KIT-positive GIST in the NHS?

How should best supportive care for this population be defined?

Are the outcomes listed appropriate? Have all the relevant outcomes been included in the scope?

Are there any subgroups of people in whom avapritinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider avapritinib will fit into the existing NICE pathway for gastrointestinal cancers?

Will the pathway differ for all subgroups in the proposed technology appraisal?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which avapritinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider avapritinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of avapritinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?

- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?

- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?

- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

[1] Patient UK (2014) Gastrointestinal Stromal Tumours. Accessed July 2019
[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 July 2019