National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	GIST Support UK	The wording specifies that it is appraising clinical and cost effectiveness but is not as specific about the marketing authorisation wording which is that it is to be authorised for: **PDGFRα D842V mutant gastrointestinal stromal tumors (GIST), regardless of prior therapy, and fourth-line unresectable metastatic GIST (regardless of mutation).**	Thank you for your comment. The wording of the remit in the scope has been amended following communication received at NICE from the company regarding the appropriate population for this indication.
	Blueprint Medicines	In the draft scope it will be very important to accurately reflect the two proposed indications within GIST, both of which have clear unmet needs as no products are currently indicated for these indications. Therefore, we suggest the following wording may better reflect how avapritinib will be used according to its initial marketing authorisation:	Thank you for your comment. The company has communicated to NICE that the population 'adult patients with

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		To appraise the clinical and cost effectiveness of avapritinib within its marketing authorisation for 2 subgroups of GIST patients: 1. In adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation, regardless of prior therapy. 2. In adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy.	unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy' is no longer appropriate for this indication. The wording in the population section of the scope has been amended accordingly.
Timing Issues	GIST Support UK	We consider this appraisal to be urgent. There are many GIST patients who either do not respond to current therapies (e.g.PDGFRA D842v mutated GIST) or who have progressed beyond the current lines of therapy that are available. The results of the Avapritinib clinical trials have been very impressive for GIST patients and we need this drug to be available to all GIST patients who need it to save their lives	Comment noted. The aim of the STA process is to provide guidance close to the marketing authorisation being granted. No action required.
	Sarcoma UK	Avapritinib is a significant advance for patients with D842V mutated GIST for whom no standard treatment was previously available. There is also no specifically-licensed medicine for wild type GIST. Therefore, timing is crucial in helping these patients.	Comment noted. See response to comment on timing issues by GIST Support UK, above.
	Blueprint Medicines	The avapritinib Marketing Authorisation Application (MAA) was submitted in July 2019. The Day 120 List of Questions is expected on November 14th, 2019, and a 3-month clock stop is anticipated. Until Day 180 (approximately at the end of April 2020), there may be additional modifications to the label	Comment noted. NICE aims to produce guidance within 90 days of marketing

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		wording, including the indication. A CHMP opinion is expected in [redacted] with formal EC Decision [redacted]. Considering the regulatory timelines for the MAA outlined above, the uncertainties related to Brexit and possible need for a separate MAA to the Medicines and Healthcare products Regulatory Agency (MHRA), and that Blueprint Medicines is a small-to-medium enterprise with a limited footprint in Europe there are limited resources to manage health technology assessment (HTA) submissions. Therefore, we respectfully suggest a submission deadline of the end of April 2020 for a NICE appraisal appropriate.	authorisation for all new drugs. The schedule for submission is set to ensure that these targets are met. No action required.

Comment 2: the draft scope

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Background information	GIST Support UK	To be accurate and complete the **emboldened text** below should be added to the Background information in the draft scope: Last sentence paragraph 2: Around 8-10% of people with GIST have no specified (wild-type) mutations and treatment options are variable**. Presently there is no standard of care for wild-type GIST and kinase inhibitors have shown limited benefit in these patients.** Paragraph 5: There are currently no lines of pharmacological therapy recommended **for patients with unresectable or metastatic KIT mutated 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	Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how the disease is managed in the population defined within the remit. This section has been amended to include that there is presently no standard of care for wild-type GIST.

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		England there are currently no approved therapies specifically for PDGFRA D842V-driven GIST. **There are no standard lines of therapy developed specifically for patients with metastatic/unresectable wild-type GIST.** **As such response to existing therapies is variable and there are currently no recommended lines of pharmacological therapy when resistance to current therapies develops/disease has progressed beyond treatment with third line therapy.**	
	Blueprint Medicines	The Background section as currently written is generally accurate.	Comment noted. No action required.
The technology/ intervention	GIST Support UK	Yes	Comment noted. No action required.
	Blueprint Medicines	The Technology section as currently written is generally accurate. For the sake of completeness, we suggest adding that avapritinib is also under investigation in the Voyager study (ClinicalTrials.gov Identifier: NCT03465722; EudraCT Number: 2017-003497-14), an open-label, randomised, Phase 3 study in patients with locally advanced unresectable or metastatic GIST (advanced GIST) of avapritinib versus regorafenib in patients previously treated with imatinib and 1 or 2 other tyrosine kinase inhibitors (TKIs). [redacted]	Thank you for your comment. The technology section has been amended to include this phase 3 trial.
Population	GIST Support UK	**No.** The populations should be listed as follows: • Adults **with KIT mutant and Wild-type** unresectable or metastatic gastrointestinal stromal tumours (GIST) who have received at least 3 prior lines of therapy.	Thank you for your comment. The company has communicated to NICE that the population 'adult

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		• Adults with unresectable or metastatic GIST and the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation regardless of prior therapy.	patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy' is no longer appropriate for this indication. The wording in the population section of the scope has been amended accordingly.
	Blueprint Medicines	The Population section correctly defines the target population, given the current NICE recommendations for other TKI therapy. Patients with PDGFRA-D842V GIST represent a distinct subgroup of patients. No currently approved TKI selectively inhibits mutations at PDGFRA D842V and there are currently no approved therapies for PDGFRA-D842V GIST.	Thank you for your comment. Please see response to comment on population by GIST support UK, above.
Comparators	GIST Support UK	Yes	Comment noted. No action required.
	Sarcoma UK	These are the standard treatments used. For those with unresectable or metastatic GIST with a KIT-positive mutation, there are 3 lines of therapy as outlined in the guidance, before receiving best supportive care. For patients with a PDGFRA-D824V mutations, there is no standard treatment available, although in practice the three lines mentioned are used simply due to lack of alternatives.	Thank you for your comment. To better reflect the current treatments for people with unresectable or metastatic GIST, the wording in this section

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		For patients with wild type mutations, the KIT+ pathway is used, but with an expectation of less response.	has been amended to state: 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'
	Blueprint Medicines	We agree that the established clinical management without avapritinib (including best supportive care) is the appropriate comparator for each target population group. Note, there are no other products licensed for either of these 2 indications.	Thank you for your comment. Please see response to comment on comparators by Sarcoma UK, above.

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Outcomes	GIST Support UK	Yes	Comment noted. No action required.
	Sarcoma UK	Yes	Comment noted. No action required.
	Blueprint Medicines	We agree that the listed outcome measures are the most relevant and important to consider.	Comment noted. No action required.
Economic analysis	GIST Support UK	The Economic Analysis section is not accurate. The marketing authorisation for Avapritinib is **for all metastatic or unresectable GIST as a fourth line treatment** rather than only those with KIT or PDGFRA mutations. **Additionally, for those with PDGFRA D842v mutations the marketing authorisation is for Avapritinib as a first line treatment**. Thus the economic modelling should be reworded to remove this specific reference but to include the associated costs of mutational testing in all patients with unresectable or metastatic GIST. Mutational testing is the recommended standard practice in the diagnostic work-up of all GISTs in the UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST).	Thank you for your comment. The company has communicated to NICE that the population 'adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy' is no longer appropriate for this indication. The population for this indication is now 'Adults with unresectable or metastatic GIST and the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation

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			regardless of prior therapy. To receive avapritinib the tumour will need to be PDGFRA D842V mutation-positive. No action required.
	Sarcoma UK	NICE guidelines suggest all patients with GIST should be referred to specialist centre with specialist pathology review. This should include mutational analysis of KIT and PDGFRA genes. As such, economic modelling should not need to include these diagnostic tests.	Comment noted. No action required.
	Blueprint Medicines	We generally agree with the economic analysis as described. However, we do not agree that 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. Furthermore, we do not agree that a sensitivity analysis should be provided without the cost of the diagnostic test. In fact, UK national guidelines recommend that D842V mutational testing is routinely performed at the 23 UK sarcoma reference centres, and at selected larger hospitals that are not officially reference centres but treat a large volume of GIST patients. As such, there would not be additional cost attributed to avapritinib. *Verbatim*, National UK GIST Guidelines (2017)[1] indicate: Page 3. “Mutational analysis has predictive value for sensitivity to molecular-targeted therapy, and also prognostic value.”	Comment noted. The scope includes standard wording about the potential inclusion of diagnostic testing costs. No action required.

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		Page 3, Key Recommendation 3. “If initial treatment is with imatinib, mutational analysis is particularly critical, since some GISTs are insensitive to the drug (e.g. PDGFRA exon 18 mutation D842V). Mutational analysis is obligatory, since some GISTs are insensitive to imatinib (e.g. those with D842V mutation in exon 18 of PDGFRA)”	
Equality and Diversity	GIST Support UK	In its current form, before the above modifications have been applied, this appraisal excludes groups of unresectable/metastatic GIST patients who are likely to benefit from Avapritinib as their fourth line therapy, and who without it have no available treatment options.	Comment noted. Please see response to comment on population by GIST Support UK, above.
Innovation	GIST Support UK	**Absolutely, yes:** • There are currently no effective treatments in the PDGFRα D842V GIST population. • Trials have reported remarkable responses when using Avapritinib in advanced GIST. • Avapritinib has suppressed complex and heterogenous mutational profiles associated with treatment-resistant unresectable/metastatic GIST. • Trials report that Avapritinib has a well-tolerated safety profile. All of these things indicate that with Avapritinib there is a huge opportunity to dramatically advance care for all GIST patients and address a significant unmet need.	Comment noted. No action required.
	Sarcoma UK	Avapritinib is a significant advance for patients with D842V mutated GIST for whom no standard treatment was previously available.	Comment noted. No action required.

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		Early data from the Phase I clinical trial has showed significant clinic benefit and ongoing durable responses for this specific subgroup - for patients with D842V mutation: ORR 84%, 96% clinical benefit rate, 12-month PFS rate 81.3%. Before this patients with D842V mutated GIST had a very poor prognosis with no standard effective therapy. Benefit has also been seen in patients with other more common KIT/PDGFRA mutations who have been through the standard treatment paradigm. This will also allow a further option for KIT+ patients who have no current standard of care after 3 lines of treatment.	
	Blueprint Medicines	Avapritinib is an innovative technology which represents a step-change in the management of unresectable or metastatic GIST. Avapritinib has the potential to have a significant impact on health-related benefits, such as reduction in tumor burden, disease stabilization and survival, for patients with fourth-line and PDGFRA-D842V unresectable or metastatic GIST. The current treatment paradigm for advanced GIST involves sequential administration of the TKIs: imatinib, sunitinib, and regorafenib. First-line treatment with imatinib is effective with a ~60% overall response rate (ORR) and median progression free survival (PFS) of 18 to 24 months.[2-6] Subsequent treatment with sunitinib in second line and regorafenib in third line is markedly less effective with a few responders (approximately 7% ORR with sunitinib[7] and 5% ORR with regorafenib)[8] and short median PFS (6 months and 4.8 months with sunitinib and regorafenib, respectively).[7,8] Once patients experience progressive disease (PD) following treatment with imatinib, sunitinib, and regorafenib, no agents are effective; therefore, fourth-line patients have an unmet medical need. No currently approved TKI selectively inhibits mutations at PDGRFA-D842V and there are currently no specifically approved therapies for PDGRFA-D842V GIST.	Comment noted. No action required.

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		With no effective treatments available, the prognosis for patients with metastatic PDGRFA-D842V GIST is dire. Published data have shown a 0% response rate and median PFS of 3-5 months with available agents in patients with metastatic PDGFRA-D842V GIST patients.[9,10] Overall survival for these patients is approximately 15 months.[9] In contrast to approved and investigational multi-kinase inhibitors, avapritinib is designed to preferentially inhibit the active conformation of KIT and PDGFRA. This allows for potent inhibition in primary mutants such as mutations at Exon 9 and 11 that shift the kinase towards its active conformation. Additionally, avapritinib is active against activation loop mutants such as KIT D816V and PDGFRA D842V with sub-nanomolar potency. Response rates to previous therapy are usually a predictor of response to subsequent therapy. [redacted] If recommended, avapritinib will offer an effective treatment option for patients with a particularly poor prognosis for whom there are no alternatives.	
Questions for consultation	GIST Support UK	The questions for consultation that have not already been addressed by the answers given above are, in the main, answered in the **UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST**) which were written by the British Sarcoma Group and form part of the NHSE National Sarcoma Service Specification.	Comment noted. No action required.
	Blueprint Medicines	Question - *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*	Thank you for your comments. The company has communicated to NICE

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		Answer - UK national guidelines recommend that D842V mutational testing is routinely performed at the 23 UK sarcoma reference centres, and at selected larger hospitals that are not officially reference centres but treat a large volume of GIST patients. "Mutational analysis has predictive value for sensitivity to molecular-targeted therapy, and also prognostic value. If initial treatment is with imatinib, mutational analysis is particularly critical, since some GISTs are insensitive to the drug (e.g. PDGFRA exon 18 mutation D842V). Mutational analysis is obligatory, since some GISTs are insensitive to imatinib (e.g. those with D842V mutation in exon 18 of PDGFRA)" (National UK GIST Guidelines – 2017)[1] Question - *Where do you consider avapritinib will fit into the existing NICE pathway for gastrointestinal cancers?* Answer – Avapritinib will be an option for the following patients: 1. As monotherapy for the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, regardless of prior therapy. 2. As monotherapy for the treatment of adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy. Question - *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?* Answer – Patients with PDGFRA-D842V GIST represent a distinct subgroup of patients. No currently approved TKI selectively inhibits mutations at	that the population 'adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy' is no longer appropriate for this indication. The wording in the population section of the scope has been amended accordingly.

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		PDGRFA D842V and there are currently no approved therapies for PDGRFA-D842V GIST. The prognosis for these patients is dire, with overall survival being approximately 15 months.[9] Avapritinib will be the first treatment available for this patient group. Results of the NAVIGATOR study have shown that avapritinib is highly effective in this patient subgroup. [redacted] Therefore, PDGFRA-D842V GIST subgroup is expected to be more clinically and cost-effective and should be examined separately.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope