NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA326; Imatinib for the adjuvant treatment of gastrointestinal stromal tumours

Original publication date:	26 November 2014
Review date	November 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA326, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'.

2. Rationale

Overall, no relevant new evidence was identified that would change the existing recommendations in TA326.

Generic versions of imatinib are now available but do not include an indication for adjuvant treatment of gastrointestinal stromal tumour (GIST). The company has confirmed that no changes in marketing authorisation are anticipated and there have not been any changes to the price.

3. Summary of new evidence and implications for review

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from January 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

In TA326 the committee recommended imatinib as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours (GIST). The summary of product characteristics states that the recommended dose of imatinib is 400 mg/day and that optimal treatment duration is not yet established. It notes that the length of treatment

in the clinical trial supporting this indication at the time of marketing authorisation was 36 months.

The table below describes 3 relevant studies. Briefly:

- A recent single-arm trial explored the effect of extending treatment with imatinib beyond 3 years. However, the results of this study are difficult to interpret because there was no comparison with the treatment duration recommended in TA326.
- There are 2 ongoing phase III trials comparing longer term imatinib treatment with the maximum treatment duration currently recommended in TA326. Both trials have limited generalisability to the NHS population because they allow dose escalation to 800 mg/day during the adjuvant treatment period, which is not the recommended dosage for this indication.

It can therefore be concluded there is currently no new evidence that would necessitate a review of TA326.

Has there been any change to the price of the technology since the guidance was published?
There are generic versions of imatinib that are now available but these are not licensed for adjuvant treatment in adults who are at significant risk of relapse following resection of GIST.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no proposed changes to the marketing authorisation that would affect the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
During the development of TA326 the committee concluded that while there was evidence that adjuvant treatment with imatinib for 3 years was more clinically effective compared with 1 year of treatment, there was uncertainty whether this benefit would continue longer term. Since the publication of TA326 in 2014, a recent abstract has reported results from a single arm trial (Raut et al 2017 PERSIST-5) that showed a benefit associated with the use of imatinib over 5 years. Evidence from this single arm trial is limited because it does not make a comparison to imatinib treatment over 3 years (currently recommended in TA326). However, there are 2 phase III open-label trials (IMADGIST and SSGXXII) that are currently in progress that compare longer term imatinib treatment with 3 years of imatinib treatment. These trials are expected to complete in 2020 and 2028 respectively and results from these trials may provide more evidence on the optimal treatment duration of imatinib. However, the

generalisability of both trials may be limited because dose escalation beyond 400 mg/day is permitted during the adjuvant treatment period.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None

4. Equality issues

No potential equalities issues were identified during scoping or the development of TA326.

GE paper sign off: **Meindert Boysen, 27 December 2017**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of imatinib within its licensed indication for the adjuvant treatment of gastrointestinal stromal tumours.

6. Current guidance

1.1 Imatinib is recommended as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours, as defined by the Miettinen 2006 criteria[1] (based on tumour size, location and mitotic rate).

1.2 People currently receiving treatment initiated within the NHS with imatinib that is not recommended for them by NICE in this guidance should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

[1] Miettinen M, Lasota J (2006) Gastrointestinal stromal tumours: review on morphology, molecular pathology, prognosis, and differential diagnosis. Archives of Pathology & Laboratory Medicine 130:1466–78.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

Imatinib is available in doses of 100 mg (60-tab pack) and 400 mg (30-tab pack) at net prices per pack of £862.19 and £1724.39 respectively (excluding VAT; 'British national formulary' [BNF] edition 67). At a dose of 400 mg per day, drug costs for a course of treatment would be approximately £20,700 for 1 year and £62,100 for 3 years.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	Yes
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Sunitinib for the treatment of gastrointestinal stromal tumours (2009) NICE technology appraisal guidance 179.
Review decision: add to the static list (January 2012)

Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (2010) NICE technology appraisal guidance 209.

This guidance updates recommendation 1.5 of TA86. All other recommendations in TA86 remain active.

Review decision: add to the static list (October 2013)

Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours (2004) NICE technology appraisal guidance 86.

Partially updated by TA209.

Review decision: add to the static list (October 2013)

In progress

Regorafenib for treating advanced gastrointestinal stromal tumours [ID1056]
Publication expected November 2017

Suspended/terminated

Masitinib for treating unresectable or metastatic gastrointestinal stromal tumours after treatment with imatinib. NICE technology appraisal guidance. Publication date to be confirmed.

Suspended because the Committee for Medicinal Products for Human Use (CHMP) has decided not to approve masitinib for treating unresectable or metastatic gastrointestinal stromal tumours after treatment with imatinib (July 2014)

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Crenolanib (Arog)	Phase 3 clinical trials UK launch expected [redacted]	[redacted]

Confidential information has been removed

3. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Imatinib has a UK marketing authorisation for the 'adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD117)-positive gastrointestinal stromal tumours (GISTs). Patients who have a low or very low risk of recurrence should not receive adjuvant treatment'. Imatinib is available in doses of 100 mg (60-tab pack) and 400 mg (30-tab pack) at net prices per pack of £862.19 and £1724.39 respectively (excluding VAT; 'British national formulary' [BNF] edition 67).	No change Source: SPC (November 2016) Glivec 100mg (60 tablets) £973.32 Glivec 400mg (30 tablets) £1946.67 Source: BNF (August 2017)

4. Registered and unpublished trials

Trial name and registration number	Details
A Randomized Multicenter Phase III Trial Evaluating the Interest of Imatinib Treatment Maintenance or Interruption After 3 Years of Adjuvant Treatment in Patients With Gastrointestinal Stromal Tumours (GIST) (IMADGIST) NCT02260505 Phase 3	Purpose: In the first arm, patients will continue imatinib treatment for 3 more years. In the second arm, patients will discontinue the imatinib treatment, as standard practice Status: recruiting No. of patients: 256 Start date: December 2014 Expected completion date: December 2020

Trial name and registration number	Details
Three Versus Five Years of Adjuvant Imatinib as Treatment of Patients With Operable GIST With a High Risk for Recurrence: A Randomised Phase III Study (SSGXXII) NCT02413736 Phase 3	Purpose: patients who have been treated with adjuvant imatinib for 3 years after surgery will be randomly allocated to receive imatinib for 2 more years or to stop imatinib Status: recruiting No. of patients: 300 Start date: May 2015 Expected completion date: May 2028
A Phase II, Non-Randomized, Open-Label Multicenter Study of 5 Year Adjuvant Imatinib Mesylate (Gleevec) in Patients at Significant Risk for Recurrence Following Complete Resection of Primary Gastrointestinal Stromal Tumor (GIST) (PERSIST-5) NCT00867113 Phase 2	Status: ongoing, not recruiting No. of patients: 91 Start date: July 2009 Expected completion date: April 2017
A Multi-center, Single Arm, Phase II Study of Adjuvant Imatinib (Glivec) in Patients Following the Resection of Primary Gastrointestinal Stromal Tumor (GIST) NCT01172548 Phase 2	Status: completed No. of patients: 132 Start date: August 2008 Completion date: March 2014 Results: Novartis registry

5. Relevant services covered by NHS England specialised commissioning

NHS England commissions specialist cancer services for adults, including services delivered on an outreach basis as part of a provider network. Specialist cancer services include

- sarcoma (except soft tissue sarcoma identified for local surgery)
- laparoscopic gastrectomy for cancer.

Source: NHS England (2016) Manual for prescribed specialised services 2016/17 Chapter 105 – specialist cancer services (adults).

NHS England (2013) 2013/14 NHS standard contract for cancer: soft tissue sarcoma (adult) B12/S/a

NHS England (2016) Clinical Commissioning Policy: Robotic assisted surgery for oesophago-gastric cancers

6. Additional information

ESMO (2014) Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Appendix D – References

Raut, C. P. et al (2017). Extended treatment with adjuvant imatinib (IM) for patients (pts) with high-risk primary gastrointestinal stromal tumor (GIST): The PERSIST-5 study. Journal of Clinical Oncology 2017 35 (15) 11009