NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RPP decision paper

Review of TA241; Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance

Final recommendation post consultation
The guidance should be transferred to the 'static guidance list'.

1. Background

This guidance was issued in January 2012.

At the GE meeting of 2 September 2014 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation was conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

TA241 should be moved to the static guidance list.

3. Rationale for selecting this proposal

No new evidence has been found that would justify a review and no there is no indication that there are any ongoing studies whose results might change the guidance.

4. Summary of consultee and commentator responses

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.

Respondent: Bristol-Myers Squibb **Response to proposal:** Agree BMS agree that this guidance should be transferred to the 'static guidance list'.	**Comment from Technology Appraisals** Comment noted. No action required.

Respondent: Novartis **Response to proposal:** Agree Novartis agrees that there is no new evidence available that is likely to lead to a change in the existing recommendations. Thus Novartis supports the proposal that TA241 should move to the static list of technology appraisals.	**Comment from Technology Appraisals** Comment noted. No action required.

Respondent: Roche Products **Response to proposal:** Agree Roche has no further evidence to suggest and furthermore has no opposition to a move to the static list .	**Comment from Technology Appraisals** Comment noted. No action required.

Respondent: Royal College of Nursing **Response to proposal:** No comment	**Comment from Technology Appraisals** Comment noted.

Respondent: National Cancer Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP) **Response to proposal:** Disagree Having reviewed the NICE Technology Appraisal guidance No.241, we strongly believe that further consideration should be given to re-appraising the drugs used for the treatment of imatinib-resistant or intolerant chronic myeloid leukaemia. There are a number of reasons for this, which are detailed below: 1. Two additional tyrosine kinase inhibitors (TKI), bosutinib and ponatinib have been licensed in the UK since this guideline was published in 2012. Along with dasatinib, these two agents have a role in the management of imatinib resistance/intolerance, albeit in a minority of patients. Therefore, it would be important to consider all four agents together for the management of imatinib resistance/intolerance. 2. There is now a European LeukemiaNet Guideline (published in 2013) which provides clear guidance on the management of imatinib resistance/intolerance (Baccarani et al, Blood 2013;122:872-884). Despite longer follow up, dasatinib and nilotinib continue to have very similar rates of complete cytogenetic response and major molecular response.	**Comment from Technology Appraisals** Comment noted. NICE has previously appraised bosutinib and it is not recommended within its marketing authorisation for treating Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) (TA299). Ponatinib underwent NICE block scoping and following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of ponatinib for treating chronic myeloid leukaemia is not appropriate, noting that the population size is very small (http://www.nice.org.uk/media/default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Block-scoping-reports/Batch-33-block-scoping-report.pdf). Bosutinib and ponatinib are also outside the remit for this review. Comment noted. No action required.

Respondent: NCRI, RCP, RCR, ACP (continued)	**Comment from Technology Appraisals**
3. For patients that develop blast phase CML on imatinib, therapeutic options are very limited as nilotinib is not licensed for blast phase disease. It would be important to reconsider dasatinib for this indication.	Comment noted. When appraising dasatinib during technology appraisal 241 the Committee noted no evidence on the use of dasatinib or high-dose imatinib given as an adjuvant treatment with intensive chemotherapy for acute chemotherapy and a very limited evidence base for blast-crisis phase of the disease. The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any of these data gaps identified by the Committee in the original appraisal.
4. There are certain types of imatinib resistance relating to BCR-ABL kinase domain mutations for which nilotinib is unsuited, e.g. Y253H and E255V. These mutations are also resistant to nilotinib at therapeutic levels and an alternative TKI would be much more suitable.	Comment noted. This is outside the remit of the current review proposal paper.
5. There are concerns emerging regarding potential vascular toxicities with nilotinib. At present, data is insufficient to suggest a change, however, there may be specific groups of patients, e.g. poorly controlled diabetics or those with pre-existing peripheral vascular disease where dasatinib would be preferable to nilotinib in terms of co-morbidities.	Comment noted. The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal or to suggest a review of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, is required.

Respondent: NCRI, RCP, RCR, ACP (continued)	**Comment from Technology Appraisals**
6. Figure 5 in Appendix B demonstrates that there is a very significant proportion of patients failing imatinib therapy as evidenced by the reduction in cost and volume of imatinib being sold. We now know that obtaining an early and deep molecular response impacts on overall survival and progression free survival. Therefore, having a choice of agents which patients could switch to guided by disease biology and co-morbidities is likely to lead to improved outcomes for CML patients. Therefore, for the above reasons, we believe consideration should be given to re-appraising guidance for imatinib resistance and intolerance.	Comment noted. Figure 5 does not provide information on the factors affecting the reduction in cost and volume of imatinib. This may reflect the recommendation that NICE does not recommend high-dose imatinib for people with Philadelphia-chromosome-positive chronic myeloid leukaemia in the chronic, accelerated or blast-crisis phase that has got worse after treatment with standard-dose imatinib (TA241). The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal.

Respondent: Royal College of Pathologists (RCPATH), British Society of Haematology (BSH) **Response to proposal:** Disagree TA241 should be reviewed and the reasons are set out below. **Current Practice** There are now four different tyrosine kinase inhibitors (TKI) licensed for the management of imatinib resistance and/or intolerance. Bosutinib, dasatinib and nilotinib are equally effective in inducing complete cytogenetic and major molecular responses in this situation. The phase II studies of bosutinib, dasatinib, nilotinib and ponatinib in imatinib failure all report complete cytogenetic response rates of the order of 50%. It is important to note that these results were obtained at a time when the patients entered into the studies might have had their disease for several years, might have failed interferon prior to being treated with imatinib and indeed might have been on imatinib with poor responses for months if not years. Although there are currently no data reporting the outcome of changing patients to an alternative TKI as soon as poor response is recognised, it is highly unlikely that their response will be worse and most likely that it will be better, as their leukaemic cells will not be allowed to proliferate with the associated risk of developing mutations. Internationally accepted guidance for the management of imatinib failure recommends all three drugs for consideration: the final choice is influenced by the presence of co-morbidities and the individual toxicity spectrum, and by the possible presence of kinase domain mutations that are responsible for resistance. Ponatinib is the only TKI capable of inducing responses in patients with a T315I mutation, an event that can occur after treatment with imatinib. Preliminary data from the phase III randomised study of imatinib versus ponatinib suggest that ponatinib is the most potent agent in the management of newly diagnosed CML: unfortunately due to the occurrence of arterial thrombotic events, the licence for this agent is restricted to use after failure of other TKI. The implication of TA241 is to limit the treatment of patients with CML to only two agents, imatinib and nilotinib, and this does not reflect medical practice and the current objectives of treatment.	**Comment from Technology Appraisals** Comment noted. NICE has previously appraised bosutinib and it is not recommended within its marketing authorisation for treating Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) (TA299). Ponatinib underwent NICE block scoping and following the consultation exercise and the scoping workshop, the Institute is of the opinion that an appraisal of ponatinib for treating chronic myeloid leukaemia is not appropriate, noting that the population size is very small (http://www.nice.org.uk/media/default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Block-scoping-reports/Batch-33-block-scoping-report.pdf). Bosutinib and ponatinib are also likely outside the remit for this review as they could be used as third line treatments, which is a different patient group than was appraised in TA241. Comment noted. The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal or to suggest a review of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, is required.

Respondent: RCPATH, BSH (continued)	**Comment from Technology Appraisals**
Evidence: chronic phase	
Since TA241 was published the goals of management of chronic myeloid leukaemia (CML) have undoubtedly altered, both in patients who are responding well to their initial tyrosine kinase inhibitor (TKI) and to those who are not. The remit of TA241 is for patients who have failed imatinib due to intolerance and resistance and both these two rather disparate groups are affected by the changes in therapy objectives.	Comment noted.
For reasons elaborated below, both patients and physicians now work to optimise molecular responses and TA241 mitigates against this. A patient who is intolerant of, or resistant to, imatinib is currently offered only nilotinib. Some patients have kinase domain mutations which render their disease resistant to nilotinib and it is therefore of little value to give them the latter drug. Furthermore, with emerging evidence of arterial thrombotic events, increased blood glucose and hypercholesterolaemia on nilotinib there are a number of patients for whom nilotinib may be contra-indicated. Since these co-morbidities are more likely to exist in an elderly population there will emerge an element of discrimination in older patients.	Comment noted. The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal or to suggest a review of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, is required.
If patients are intolerant of or resistant to nilotinib there is no provision in NICE guidance for them to try one or more of the remaining 3 TKI, to which they stand a good chance not only of responding but also of tolerating in the long-term	
• There is now a large body of evidence to demonstrate that patients who respond well to their TKI therapy will have a normal or near normal life expectancy. We have known for 10 years that the survival of patients who achieve complete cytogenetic responses is excellent (approximately 90% at 5 years without any correction for the expected death rate in an age matched population). Because the overall survival of this group is so good it has been difficult to demonstrate the effect on survival, if any, of deeper responses. In the last 2-3 years longer follow-up of early studies has shown that the best survival is achieved by patients with the deepest responses, as measured by molecular assays, i.e. RQ-PCR.	Comment noted. No action required.

Respondent: RCPATH, BSH (continued)	**Comment from Technology Appraisals**
• Since 2011 a number of studies have shown that patients destined to respond well and durably can be identified as early as 3 months after starting a TKI, if they have achieved a RQ-PCR <10%. This observation applies equally well to any TKI and importantly for this guidance, to responses to first, second, third and fourth line treatment. This means that a patient who fails several lines of treatment, for whatever combination of reasons, may still have an excellent survival on another TKI and that this can be identified 3 months after starting the final TKI.	Comment noted. The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal.
• It is also important to note that although a RQ-PCR result <10% at 3 months identifies a group of patients with an excellent prognosis, patients with a RQ-PCR >10% do not necessarily have a poor prognosis. In fact the difference in overall survival at 5 years in the German CML IV study is only 7%. This is because many of the patients with a RQ-PCR >10% are responsive to an alternative TKI. This therefore becomes a very important reason why patients should be allowed to try alternative TKIs before assuming that they will not be excellent responders.	Comment noted. No action required.

Respondent: RCPATH, BSH (continued)	**Comment from Technology Appraisals**
• Some patients who respond exceptionally well to their TKI, as defined by a durable 4.5 log molecular remission, again measured by RQ-PCR, can discontinue drug indefinitely. This evidence emanates from a number of clinical trials in both first and second generation agents and from case reports of patients who stopped treatment either because of side effects or because of pregnancy. This observation has had a fundamental impact on the goals of treatment in that the ability to stop treatment is a welcome advance both for the quality of life of the patient, with reduction in side effects and the concomitant need for supportive care and in the cost of long-term care. Several estimates of the likeliness of deep and durable responses are now published. The Adelaide group predict that 37% of patients treated with imatinib from diagnosis will reach this response after 8 years of therapy and that some 40% of these will be able to stop drug indefinitely. The German CML IV study group which trialled imatinib 400mg against imatinib 800mg or imatinib 400mg in combination with interferon have shown a higher figure of 71% at 9 years. It is worth noting in the context of TA241 that the best responses were in patients randomised to imatinib 800mg. If 40% of this group can stop treatment indefinitely the total figure will rise to some 30% of all patients, with a very substantial saving in on-going drug costs. The use of the second generation drugs for newly diagnosed patients reach similar levels of MR 4.5 as high dose imatinib.	Comment noted. In appraisal TA241 the Committee concluded that high-dose imatinib was dominated (that is, more expensive and less effective than another treatment) in all models provided during the appraisal. Imatinib plus interferon is outside the remit of this review proposal paper.
• Finally within this guidance, there is no acknowledgement that patients may fail imatinib and/or nilotinib because of the presence of kinase domain mutations that render their disease resistant to both drugs. These mutations may however be sensitive to bosutinib, dasatinib and/or ponatinib and it is inexplicable why a patient who fails imatinib with a nilotinib resistant but dasatinib sensitive mutation is offered nilotinib. Not only in the treatment ineffective and expensive but it places the patient at risk of disease progression.	Comment noted. The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal.

Respondent: RCPATH, BSH (continued)	**Comment from Technology Appraisals**
Taking all these data into account it appears that the vast majority of patients diagnosed with CML in 2014 can have a normal life expectancy. In fact, in order to make a difference to the remaining 10-15% of patients who will not respond to (or be unable to tolerate) any TKI It is important that they are given successive trials of TKIs either depending on their response at 3-6 months, or on their ability to tolerate the drugs. Any patient identified as a poor responder should be referred for early transplant to reduce the risk of developing advanced phase disease. It is therefore very unclear from a medical perspective why a patient who fails imatinib because of resistance and/or intolerance should be allowed only one other agent before effective medical treatment is abandoned. It is entirely possible to fail both imatinib and nilotinib through any combination of resistance and intolerance and still have a chance of responding to another agent. The best evidence for this comes from the phase II studies of dasatinib and nilotinib for imatinib resistance and/or intolerance, in which 70% of patients had discontinued their study drug by 4 years, yet overall survival remained very good, certainly in excess of that expected from the previous gold standard of interferon. The reality of patient management is that many patients will require more than one change of TKI before they find a drug that is not contra-indicated and well tolerated in the long-term. Dasatinib, bosutinib and ponatinib are just as effective as nilotinib in patients failing imatinib for any reason, so the rationale of a guidance that favours nilotinib over the alternative drugs is not justified. All four second and third generation drugs have different side effects in different patients and the ability to change a drug until the combination of acceptable toxicity and efficacy is achieved, is most welcome.	The studies identified during the literature searches for this review proposal paper did not provide evidence to fill any data gaps identified by the Committee in the original appraisal or to suggest a review of dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance, is required.

Respondent: RCPATH, BSH (continued) **Evidence: Advanced Phase Disease** With respect to patients who fail imatinib for any reason and then progress to blast crisis, this guidance does not permit them another TKI since nilotinib is not licensed for blast crisis. This is unjustifiable. Return to a second chronic phase induced by an effective TKI and followed by stem cell transplantation is associated with an overall survival of 35-40%. The favoured TKI in blast crisis is Dasatinib because it is the only TKI to cross the blood brain barrier, an important feature in a disease with a propensity to central nervous system involvement.	**Comment from Technology Appraisals** Comment noted. During the appraisal the Committee heard from the clinical specialists that treatment strategy in the blast-crisis phase of the disease is different from that in the accelerated or chronic phases, with dasatinib and high-dose imatinib given as adjuvant treatment with intensive chemotherapy for acute leukaemia. The studies identified during the literature searches for this review proposal paper did not provide evidence on switching TKIs.

Paper signed off by: Janet Robertson, 11 January 2016

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