National Institute for Health and Clinical Excellence

Dasatinib for acute lymphoblastic leukaemia

Responses to comments received during draft scope consultation

Section	Consultee	Comment	Response
Draft remit: Appropriateness	BMS	BMS does not believe that it is appropriate for this topic to be referred to NICE for an appraisal at this stage. Data on efficacy of dasatinib in patients with Ph+ ALL is extremely limited and immature. Further, the number of eligible patients is extremely small (adult Ph+ ALL resistant/intolerant to prior therapy is an ultra-orphan condition, according to the NICE criteria). Therefore, the appraisal should be reconsidered to reflect available evidence.	The Institute has not been instructed to appraise ultra-orphan drugs differently from other technologies. The appraisal will use the available evidence – guidance is required following licensing to avoid variations in access to new drugs
	BCSH / RCPath (1)	It is appropriate to look at dasatinib but since this is early in its development there may be a case for early review if the findings are negative as more data may emerge.	Comment noted
	Cancerbackup	Yes	Comment noted
	BSCH / RCPath (2)	Appropriate to consider for relapsed/resistant Ph pos ALL or with known imatinib-resistance bcr-abl mutations or in patients intolerant of other ALL therapies.	Comment noted
Wording	BMS	No. The wording should reflect dasatinib's licensed indication, which is "treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy"	The remit has been amended to make clear that dasatinib will be appraised within its licensed indication
	BCSH / RCPath (1)	The treatment described is incorrect and needs review. HyperCVAD is not routine treatment in the UK. Imatinib WITH chemotherapy (except in the elderly) is likely to be first line therapy currently. Dastainib will only be used after relapse and some of these patients will be palliative	Scope amended

		where its use would be inappropriate. Some patients who have not been considered for Allogeneic BMT in CR1 may be considered for AlloBMT in second response -it is likely that these patients would represent the best candidates for Dasatinib and I would suggest that this is considerd in the scoping meeting.It is likely that this would also be in combination with chemotherapy eg FLAG or FLAG-Ida	
	BSCH / RCPath (2)	The title and initial wording does not make it clear that this is under consideration for relapsed or resistant Ph pos ALL and not for de novo disease. For de-novo disease, clinical trials of dasatinib are on-going	Scope amended. The drug will be appraised in line with its marketing authorisation
Timing issues	BMS	BMS does not believe that it is urgent for this topic to be referred to NICE for an appraisal at this stage. Data on efficacy of dasatinib in patients with Ph+ ALL is extremely limited and immature and the number of eligible patients is extremely small (adult Ph+ ALL resistant/intolerant to prior therapy is an ultra-orphan condition, according to the NICE criteria).	Comment noted (see above)
	BCSH / RCPath (1)	Not urgent, in fact delay might allow the emergence of new data.	Comment noted
	Cancerbackup	Yes	Comment noted
	BSCH / RCPath (2)	There is evidence that dasatinib is of value in the situation for which it is being proposed. See above re wording of title and wording within the document.	Comment noted
Draft scope:	BMS	The section is brief but generally accurate. Last sentence should read: Other than dasatinib, therapeutic options	Consultees at the scoping workshop indicated other

Background information		following resistance to imatinib are "non-existent" (instead of limited)	available treatment options and these have been included in the list of comparators.
	BCSH / RCPath (1)	Poorly written -needs complete rewrite	Comment noted
	Cancerbackup	It is accurate	Comment noted
	BSCH / RCPath (2)	"Adult" is inappropriately defined. Most people would not regard anyone aged 15 as an adult for ALL therapy purposes. There is considerbale disagreement over this, so the document needs to reflect that.	Scope amended
		The comment about 'first line treatment' is very inaccurate "first line treatment:" is not 'usually' with hyperCVAD. There are a variety of ALL induction regimens in place around the world, all of which have similar efficacies to hyperCVAD.	Scope amended
		The description of the use of Imatinib is inaccurate. Imatinib is commonly ADDED to induction chemotherapy (not given instead of, except in the very elderly). The long term efficacy of imatinib in this disease is unclear and there are a lot of treatment failures - the reasons are not completely clear and resistance to imatinib may be a factor but this is not clear.	Scope amended
		However, it is inaccurate to state that data clearly show 'that over 90% of patients with ALL become resistant to imatinib" -those types of data are only beginning to emerge.	Scope amended

		Standard therapy for younger patients is to have an allogenic bone marrow transplant in first remission. This is not mentioned.	Scope amended
Technology/ intervention	BMS	The description is accurate.	Comment noted
	BCSH / RCPath (1)	Need to address use in combination with chemotherapy	Dasatinib will be appraised according to its marketing authorisation
	Cancerbackup	Yes	Comment noted
	BSCH / RCPath (2)	Basically accurate - if one knows what they are trying to say. But is is extremely poorly written and described, so that someone who does not know what this is about would not get an accurate picture of the differences between imatinib and dasatinib.	Scope amended
Population	BMS	Yes	Comment noted
	BCSH / RCPath (1)	Yes Focus on patients suitable for Allo BMT	no particular subgroups were identified at the scoping workshop and therefore none are included in the scope
	Cancerbackup	The population is well defined	Comment noted
	BSCH / RCPath (2)	It is not the people who are resistant to therapy is it their leukaemia For patients with disease which has relapsed or is resistant to therapy this is very obvious and easily	Scope amended Comment noted

		defined. Patients who are "intolerant" to other therapies could be a harder group to define. It would be reasonable to state some criteria.	Comment noted
Comparators	BMS	The comparators should be: bone marrow transplant and imatinib 600mg/day.	These are now included as comparators
	BCSH / RCPath (1)	Measure achievement of second remission	This does not constitute a comparator
	Cancerbackup	There are no comparators. It is appropriate to mention that no active treatment is the alternative.	Consultees at the scoping workshop indicated other available treatment options and these have been included in the list of comparators.
	BSCH / RCPath (2)	It is true that once people with ALL especially Ph pos ALL have relapsed, there is no known effective salvage therapy.	Consultees at the scoping workshop indicated other available treatment options and these have been included in the list of comparators.
Outcomes	BMS	1. Hematologic response should be removed as it is misleading in Ph+ ALL, where a patient can have a real response without achieving hematological response. 2. Adverse effects of treatment should be re-phrased as discontinuation due to adverse effects.	Haematologic response was agreed at the scoping workshop to be a valid outcome. The adverse effects considered in the appraisal will not be limited to those that necessitate treatment

			withdrawal
	BCSH / RCPath (1)	yes	Comment noted
	Cancerbackup	Yes	Comment noted
	BSCH / RCPath (2)	Yes One outcome which is not mentioned is documenting the bcr-abl mutations which make the ALL resistant to imatinib	Comments noted This is not a clinical outcome
Economic analysis	BMS	No comment	Comment noted
	Cancerbackup	As population indication also covers people who are intolerant to prior therapy, will the economic analysis reflect prior side effect management/ morbidity costs which necessitated change to Dasatinib?	Such costs would be common to all patients and would not affect a cost-effectiveness analysis of dasatinib
	BSCH / RCPath (2)	Can't comment. Most patients with relapsed Ph pos ALL would be dead within 3 months without therapy.	Comment noted
Equality	BMS	No comment	Comment noted
	BSCH / RCPath (2)	Not applicable	Comment noted
Other considerations	BMS	BMS believes that, if this appraisal proceeds, the additional criteria for ultra-orphan medicines, as defined by NICE, should be explicitly included and consider in this appraisal.	The Institute has not been instructed to appraise ultra-orphan drugs differently from other technologies
Questions	BMS	Question 1:	

		Given the extremely small number of patients with Ph+ ALL eligible for dasatinib treatment, it is not possible to define any sub-groups. Question 2: The appropriate comparators for dasatinib in this appraisal are bone marrow transplant and imatinib 600mg/day Question 3: Current arrangements for testing for the presence of the Philadelphia chromosome vary throughout the UK but usually involve simple cytogenetics or FISH at initiation and PCR during follow-up. Question 4: In line with its marketing authorisation, dasatinib is used as monotherapy	Comment noted These are now included as comparators Comment noted Comment noted
	BSCH / RCPath (2)	Dasatinib would be a last-ditch attempt to save someone's life in the proposed situation. Available data suggest some responses would be seen with modest toxicity but without a definitive therapy, cure would be unlikely. The best use of the drug would likely be earlier in the disease and ongoing trials are evaluating this. In relapsed Ph pos ALL, there aren't any really appropriate comparators except standard chemotherapy. If the patient has already had a bone marrow transplant, even standard chemotherapy would be difficult to administer (and also futile).	Dasatinib will be appraised within its licensed indications Consultees at the scoping workshop indicated other available treatment options and these have been included in the list of comparators

		Bcr-abl is readily determined and quantified in a number of laboratories in the UK. Analysis of bcr-abl mutations is limited to a smaller number of labs.	Comment noted
Additional comments	BCSH / RCPath (2)	It was not very well written both grammatically and scientifically. Surprised it is not referenced.	Comment noted. References are not included in technology appraisal scopes