National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Decitabine for the treatment of acute myeloid leukaemia

Response to consultee and commentator comments on the draft remit, draft scope and provisional matrix

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Janssen-Clag	No comment	Comment noted, no action required.
	The Royal College of Pathologists and British Society for Haematology	Yes	Comment noted, no action required.
Wording	Janssen-Clag	The wording of the remit reflects the issue of clinical and cost-effectiveness about Decitabine.	Comment noted, no action required.
	The Royal College of Pathologists and British Society for Haematology	The intervention is aimed at a serious unmet need and the remit is a good reflection of the position with some minor commets see below	Comment noted, no action required.
Timing Issues	Janssen-Clag	No comment	Comment noted, no action required.

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	The Royal College of Pathologists and British Society for Haematology	there is no randomised data although the company has completed recruitement to a randomised trial in november 2009. i do not expect the data to be out until early 2011. The company may not even persist if this trial is negative. There is unrandomised data but it is not my view that this should be considered since that it unlikley to be a basis for regulatry approval the drug is already quite widely used in the US and in some parts of Europe for whivh there is modest evidence base and no randomised data against an accepted standard of care	Comment noted. The timing of the appraisal will take into consideration availability of evidence.
Additional comments on the draft remit	Janssen-Clag	No comment	Comment noted, no action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Janssen-Cilag	No comment	Comment noted, no action required.
	Royal College of Pathologists BSH and NCRI	I think significant detail is lacking here, patients over the age of 60 come into 3 major groupings. The first grouping is patients approximately in the age of 60-75 years, many of these patients are fit for intensive chemotherapy and that would be the standard of care at many UK centres. Exceptions to this would be if the patient has any significant co-morbidities which could preclude their having intensive chemotherapy such as pre-existing severe cardiac, renal or pulmonary disease. Intensive chemotherapy within this age group have an approximately 60-65% chance of achieving complete remission based on information for the NCRN AML16 trial for elderly AML. Some patients achieving CR are also candidates for alternative therapies such as reduced intensity allogeneic transplantation as is being explored in AML16 although this would only be explored in patients aged 60-70 years. The second group of patients is patients considered unfit for intensive chemotherapy, this age group is approximately 75 years+ although some younger patients may be so treated if they have significant co-morbidities. In the UK the standard of care for these patients that has emerged following the	Comment noted. Background information in the draft scope is a brief summary for information only. These details have now been highlighted in the draft scope as subgroups.

Section	Consultees	Comments	Action
		results of the MRC AML14 trial has been low dose Ara-C (LDAC) which was shown to significantly improve the survival compared to best supportive care including the use of oral Hydroxyurea therapy. With LDAC approximately 18% of patients will achieve a CR and those patients achieving a CR will have a significant prolongation of survival. Although these results are superior to best supportive care / Hydroxyurea they are still clearly unsatisfactory and we need new options to improve the response rate and prolong the survival of the elderly frail group of patients with AML. Such a strategy is being in the NCRN AML16 trial of non intensive therapies where a number of novel therapies are being compared against the 'gold standard' of low dose Ara-C. Finally there is a 3rd group of patients who may be too old and frail even to consider non intensive chemo therapeutic options (or who decline this approach) and for these patients the treatment would comprise best supportive care which would be blood and platelet transfusions until the patient succumbs to the disease.	
	The Royal College of Pathologists and British Society for Haematology	Accurate	Comment noted, no action required.
The technology/ intervention	Janssen-Clag	No comment	Comment noted, no action required.
	Royal College of Pathologists BSH and NCRI	For the reasons above I found this inadequate. The comparator group is not well defined. It should include conventional chemotherapy	Comparators in the draft scope have now been amended accordingly.
	The Royal College of Pathologists and British Society for	Accurate	Comment noted, no action required.

Section	Consultees	Comments	Action
	Haematology		
Population	Janssen-Clag	No comment	Comment noted, no action required.
	Royal College of Pathologists BSH and NCRI	. As discussed above the population of patients over the age of 65 with AML comprise at least 3 different groups as defined above. Therefore NICE needs to be clear as to which comparator group it is actually comparing the novel technology with.	Population in the draft scope has now been amended to accurately reflect the eligible population.
	The Royal College of Pathologists and British Society for Haematology	accurate this is a potential treatment for older patients for whom intensive treatment may not be considered suitable	Comment noted. Population in the draft scope has now been amended to accurately reflect the eligible population.
Comparators	Janssen-Clag	Low dose cytarabine is the main non-intensive chemotherapy recommended for the treatment of acute myeloid leukaemia in the elderly. Hydroxycarbamide, etoposide and 6-mercaptopurine could be considered as alternative comparators provided that there is sufficient evidence available. Best supportive care is defined as treatment given with the intent to maximize quality of life without a specific antileukemic intent. It includes treatment with anibiotics and anifungal agents, blood transfusions and nutritional support.	Comment noted. Hydroxycarbamide, etoposide and 6-mercaptopurine have now been grouped under best supportive care in the draft scope.
	Royal College of Pathologists BSH and NCRI	I have discussed this above under 'Background'. To my knowledge it needs to be clearly defined which therapeutic patient group the novel technology is being compared against. 1) Intensive therapy, 2) Low dose chemotherapy 3) Best Supportive Care but as pointed out above BSC is really only used as palliative treatment for very elderly and frail patients.	Comment noted. Population and subgroups have been amended appropriately in the draft scope.
	The Royal College of Pathologists and British Society for	These are correct. There is in the UK a national trial just completed where low dose clofarabine and Low Dose Ara-C + my;otarg are comparators. You may not accept unlicensed comparators. Azacitidien has approval for this patient group within the subgroup who have 20 - 30% blasts in the bone marrow at diagnosis. Again it is not licensed beyond that although some will use it.	Comment noted. Clofarabine has now been included as a comparator.

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	Haematology	Best supportive care is a valid comparator at the moment. This is ususally understood to mean patient support with blood and blood products and antibiotics as required. Patients may receive hydroxyurea but only to control the leukaemic counts in the blood with not intention that it will achieve disease remission. In this respect Hydroxyerea is usually used but this would also be the context where etopiside and 6mp would be used. Low dose Ara-c is a definitive treatmetn which has been shown in randomised trialin the Uk to be better than best supportive care/i	Hydroxycarbamide, etoposide and 6-mercaptopurine have now been grouped under best supportive care.
Outcomes	Janssen-Clag	Remission rate is the appropriate term to be used in leukaemia and should replace 'response rate'. Blood-transfusion independence and hospitalizations are additional outcomes that need to be considered as they will capture important health benefits of decitabine.	Comment noted. Consultees considered that remission rate and response rate reflect the same outcome in this patient group. The draft scope has not been amended.
	Royal College of Pathologists BSH and NCRI	These are OK	Comment noted, no action required.
	The Royal College of Pathologists and British Society for Haematology	This sort of drug will not improve CR which is usually a good surrogate for survival benefit, i.e a drug is unlikley to be better if it does not improve CR. Paradoxically just because a patients gets a CR does not becessarily mean that they wiil survive bette. a toxic treatmetn may get more CRs but they die early. This is a different frug, where the concept is not to increase CR although there will be some CRs, but to improve overall survival even although the patietn does not get a CR.So your assessment should be heavily focussed on survival	Comment noted, no action required.
Economic analysis	Janssen-Clag	No comment	Comment noted, no action required.
	The Royal College of Pathologists and British Society for	Apprpriate	Comment noted, no action required.

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	Haematology		
Equality and Diversity	Janssen-Clag	No comment	Comment noted, no action required.
	The Royal College of Pathologists and British Society for Haematology	cost willlimit access…..is that an equality issue?	Comment noted. The appraisal will consider both costs and efficacy of the technology.
Kennedy Report Question – Innovation	Janssen-Cilag	We consider the following outcomes/benefits as being relevant for decitabine in comparison to best supportive care or low dose cytarabine: overall survival, complete remission, time to response, frequency of use, frequency of hospitalization, hospital stay, transfusion requirements, 30-day mortality.	Comment noted, no action required.
	Janssen-Cilag	The following data is available to enable the appraisal committee to take account of the above benefits: - one phase II, open label, single arm trial (NCT00866073) - one phase III, randomized, open label (NCT00260832)	Comment noted, no action required.
Other considerations	Janssen-Cilag	No comment	Comment noted, no action required.
	The Royal College of Pathologists and British Society for Haematology	None	Comment noted, no action required.
Questions for consultation	Janssen-Clag	Although intensive chemotherapy can be justified for some elderly patients, the majority of them do not receive intensive chemotherapy due to the induction mortality rate and elevated associated toxicity. Decitabine provides a non-intensive alternative for elderly patients with expected greater activity and	Comment noted. Consultees agreed that elderly people who are unfit for intensive chemotherapy will receive non

Section	Consultees	Comments	Action
		efficacy than the currently available non-intensive options for this difficult-to-treat population.	intensive chemotherapy. The appraisal will take into consideration the efficacy of the technology.
	The Royal College of Pathologists and British Society for Haematology	None	Comment noted, no action required.
Additional comments on the draft scope.	Janssen-Clag	No additional comment	Comment noted, no action required.

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

Department of Health

Macmillan Cancer Support

Marie Curie Cancer Care

Napp Pharmaceuticals

NHS Quality Improvement Scotland

Royal College of Nursing

Research Institute for the Care of Older People

Welsh Assembly Government

Comment 2: the provisional matrix

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	Add Allied Health Professionals Federation	NICE Secretariat		Added	Allied Health Professionals Federation meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.
2.	Add Care Quality Commission	NICE Secretariat		Added	Care Quality Commission meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.

2.	Add NHS Commercial Medicines Unit to general group commentators.	NICE Secretariat		Added	NHS Commercial Medicines Unit meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a general group commentator.
3.	Remove Policy Research Institute for Ageing and Ethnicity	NICE Secretariat		Removed	This organisation has requested to be removed from all matrices.
4.	Add Cancer 52 to patient/carer groups.	NICE Secretariat		Added	Cancer 52 meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a patient/carer group.
5.	Add Cochrane Haematological Malignancies Group to relevant research group commentators.	NICE Secretariat		Added	Cochrane haematological malignancies group meets the inclusion criteria and has a close interest in this appraisal topic therefore this organisation has been added to the matrix as a research group commentator.

6.	Remove Chinese National Healthy Living Centre	NICE Secretariat		Removed	This organisation has requested to be removed from all matrices.
7.	Remove CANCERactive	NICE Secretariat		Removed	CANCERactive have now closed, and therefore been removed from the matrix.
8.	Remove National Cancer Alliance	NICE Secretariat		Removed	National Cancer Alliance have now closed, and therefore been removed from the matrix.