National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Romidepsin for the treatment of relapsed or refractory peripheral T-cell lymphoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Celgene	Peripheral T-cell lymphoma has been designated as an orphan disease with a high unmet need. Celgene agrees with NICE regarding the significance of a technology like romidepsin for this condition, however, given the small patient population (who would otherwise be treated with a mix of unlicensed single agent or combination therapies or enrol into clinical trials), we do not think it appropriate for NICE to appraise this topic.	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise romidepsin.
	Lymphoma Association and Leukaemia CARE	There is very little available for this patient group so it is important that new technologies are assessed in a way that enables patients to access potentially effective treatments as quickly as possible.	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Yes. Peripheral T cell lympoma is a disease for which new therapies are urgently required.	Comment noted.

Section	Consultees	Comments	Action
Wording	Celgene	The expected license for romidepsin is for the treatment of [redacted]. However, discussions with the EMA [redacted]	Comment noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Yes.	Comment noted.
Timing Issues	Celgene	In light of [redacted] Celgene is of the view that romidepsin should not be subject to a NICE appraisal.	Comment noted. Following discussion at the scoping workshop it was agreed that it was appropriate to seek a formal referral to appraise romidepsin.
	Lymphoma Association and Leukaemia CARE	The technology has not yet received its marketing authorisation and there is little clinical trial data currently available. The Phase II trial data available is encouraging and early access to this technology could save or extend lives in a group of patients where the current treatment options are of limited benefit or only supportive.	Comment noted.

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	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Moderate.	Comment noted.
Additional comments on the draft remit	Celgene	Patient numbers eligible for treatment with romidepsin are likely to be low. The expected indication for romidepsin is for relapsed and refractory patients and the draft scope mentions that around 1000 patients are diagnosed with PTCL. There remains uncertainty around the exact number of patients with PTCL, but a recent analysis by the Haematological Malignancy Research Network (HMRN) in York (on Celgene's request) estimated an age adjusted incidence rate for PTCL (common, & nos) to be 0.7/100,000 population.	Comment noted. Following discussion at the scoping workshop it was agreed that the patient population was likely to be small but noted that other appraisals have looked at smaller populations and therefore it would also be appropriate to consider this topic.
	Lymphoma Association and Leukaemia CARE	No comment.	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	No.	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Celgene	PTCL is a life threatening condition with a median survival of approximately 2 years. Therapy options used in the clinical practice for relapsed or refractory PTCL are unlicensed and the limited available evidence comes from small clinical trials with inconclusive results.	Comment noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Accurate and complete following changes made to (attached) document in wordtracker: They are broadly described as either Hodgkin's lymphoma or non-Hodgkin's lymphoma. Peripheral T-cell lymphoma (PTCL) **comprise** a group of rare and aggressive non-Hodgkin's lymphomas that develop from T-cells in different stages of maturity. By the time the condition is diagnosed, most people have widespread disease, and experience fever, fatigue, weight loss and night sweats, and require **immediate** treatment to manage their condition. **Compared with other types of non-Hodgkin lymphoma the prognosis for patients with PTCL is poor** with an estimated five year survival rate after first-line therapy **of** 30%.	Comment noted. The background section has been updated to include the first proposed change. However as the background section is only intended to provide a brief description of the disease and current management options, none of the other changes have been included. More complete information will be provided by the manufacturer in their submission once the appraisal begins.

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		There is therefore an urgent need for new and effective treatments in this disease where unfortunately there has been little progress over the last two decades.	
The technology/ intervention	Celgene	We request the description to change to "romidepsin is in a new class of histone deacetylase (HDAC) inhibitors for the treatment of PTCL. HDAC inhibitors induce the acetylation of both histones and other proteins, resulting in antitumour activity due to increased tumour suppressor gene transcription, growth inhibition, cell-cycle regulation, and apoptosis.	Comment noted. The technology section in the scope is only intended to provide a brief description of romidepsin. More complete information will be provided by the manufacturer in their submission once the appraisal begins. No changes to the scope have been made.
	Lymphoma Association and Leukaemia CARE	No comment.	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Yes	Comment noted.
Population	Celgene	No comments	Comment noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Comment noted.

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	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Yes. No subgroups to be considered seperately	Comment noted.
Comparators	Celgene	There is currently no standard treatment alternative for patients with relapsed or refractory PTCL. Regardless of the number of prior therapies, little research effort has been undertaken to establish treatment standards. Due to an unmet medical need, the National comprehensive Cancer Network (NCCN) guidelines suggest clinical trial participation as the preferred option in relapsed/refractory PTCL (NCCN, 2010). Evidence from other existing Phase I/II trials is inconclusive due to a number of confounding factors such as limited number of patients, and inclusion of mixed T-cell populations and lack of sufficient follow up.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, the reliability of the available evidence will be considered by the Committee when formulating its recommendations.
	Lymphoma Association and Leukaemia CARE	There are no direct standard comparator studies and no standard treatment for this group of patients. Pralatrexate is not yet used in the UK so it is difficult to see how it could be used as a comparator at this stage.	Comment noted. The scoping workshop heard that pralatrexate would only be included as a comparator for romidepsin if it became routinely used as a treatment option within the NHS before an appraisal of romidepsin begins. Since the scoping workshop, the appraisal of pralatrexate has been

Section	Consultees	Comments	Action
			suspended because pralatrexate received a negative CHMP decision. Therefore pralatrexate will not be included as a comparator for romidepsin.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Accurate and complete following changes made to document in wordtracker: People with relapsed or refractory PTCL receive a variety of second-line and subsequent treatments, most commonly multi-agent chemotherapy that may be platinum **or gemcitabine** based. **High dose chemotherapy with autologous stem cell rescue may be used as a consolidation step if first or second remission can be achieved and the patient is considered fit enough to withstand this type of treatment.** Best supportive care (which may include single-agent	Comment noted. Comment noted. Single and combination treatment regimens that may include platinum-based chemotherapy (such as carboplatin or cisplatin) and/or other chemotherapeutic agents (such as cytarabine, epirubicin, etoposide, fludarabine, gemcitabine, ifosamide or lomustine are already listed as comparators in the scope. Comment noted. During the scoping workshop it was discussed whether autologus stem cell rescue should be added as a comparator. It was clarified by the NICE technical team that comparators within the scope are those treatments that would possibly be displaced by romidepsin if

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		chemotherapy, **corticosteroids or radiotherapy** for symptomatic relief)	it was approved. It was the clinical specialist's view that romidepsin would not displace stem cell transplants for PTCL. Therefore it has not been included as a comparator in the scope. Comment noted. Single agent chemotherapy and corticosteroids are already listed as comparators in the scope. At the scoping workshop, consultees did not consider that radiotherapy is routinely administered for symptomatic relief. Therefore it was not included as a comparator.
Outcomes	Celgene	The trials supporting the expected license indication are single arm open label studies. OS was not an endpoint either primary or secondary. Health related quality of life data was not captured in the studies. Achievement of complete response, especially response of significant duration is a benefit to patients as there is associated resolution of tumour burden with reduction in lymphadenopathy, organomegaly, skin lesions, and bone marrow involvement. Clinical benefit of response was supported by the finding that patients who achieved complete response had a markedly longer disease-free period with longer TTP and PFS compared to all other response categories.	Comment noted. The scoping workshop attendees heard that the outcome measures included in the draft scope were typical measures for cancer topics. It was agreed that no changes to the outcome measures within the draft scope were required.

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	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Yes	Comment noted.
Economic analysis	Celgene	Given the rarity of the condition, the availability of trial evidence, lack of clarity on comparator treatments, and the likely uncertainty around clinical and cost-effectiveness using conventional criteria, we do not consider this topic to be suitable for a technology appraisal.	Comment noted. If this topic is formally referred to NICE as a technology appraisal, the reliability of the available evidence will be considered by the Committee when formulating its recommendations.
	Lymphoma Association and Leukaemia CARE	As there are very limited alternatives for these patients, it is desirable, assuming UK marketing authorisation is approved, that patients should have access to this technology as soon as possible.	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer	Our main concern is rejecting a drug that has clear benefit for some individuals but doesn't satisfy the overall QALY analysis. Guidelines around starting the drug in all eligible patients but only continuing if demonstrable benefit in tumour volume reduction and/or quality of life after say 6-8 weeks would be fair and rational	Comment noted. If this topic is formally referred to NICE as a technology appraisal, the Committee will consider all available evidence when formulating its recommendations. Any

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	Physicians, and Joint Collegiate Council for Oncology		additional benefits of romidepsin which are not captured in the QALY calculation will also be considered by the Committee.
Equality and Diversity	Celgene	The median age of PTCL diagnosis has been estimated to be 70.4 yrs and affects mostly elderly populations.	Comment noted. It was agreed at the scoping workshop that the age of people at diagnosis is unlikely to affect their access to romidepsin, therefore this is not a specific equality issue.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	Guidelines as outlined above	Comment noted.
Innovation	Celgene	No comment.	Response noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma	No comment.	Response noted.

Section	Consultees	Comments	Action
	Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology		
Other considerations	Celgene	No comment.	Response noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	No.	Comment noted.
Questions for consultation *How is relapsed or refractory peripheral T-cell lymphoma currently managed in clinical practice?*	Celgene	No comment.	Response noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists,	No comment.	Response noted.

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• *Have the most appropriate comparators for the treatment of relapsed or refractory peripheral T-cell lymphoma been included in the scope?* • *What does best supportive care consist of?*	Association for Cancer Physicians, and Joint Collegiate Council for Oncology		
Questions for consultation *Are there any subgroups of patients in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?*	Celgene	No comment.	Response noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	No comment.	Response noted.
Questions for consultation	Celgene	No comment.	Response noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.

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Are there any issues that require special attention in light of the duty to have due regard to the need to eliminate unlawful discrimination and promote equality?	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	No comment.	Response noted.
Questions for consultation *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?*	Celgene	A phase 2b, single-arm, open-label, multicenter trial by Coiffer et al assessed the efficacy and safety of romidepsin in 131 patients with PTCL who had failed at least 1 course of prior systemic therapy (Coiffer 2010). Of the 130 patients with histopathologically-confirmed PTCL, ORR was documented in 25% (33/130) of patients; The median DOR was 17 months (range, <1 to 34+ months) among all responders.	Comment noted.
	Lymphoma Association and Leukaemia CARE	We are aware of recent Phase II trial data (Blood, 2011) that show a promising overall response rate (38%) and manageable toxicity. 18% of patients achieved complete responses with a median duration of 29.7 months (range 3 - 74). 20% achieved partial responses with a median duration of 5.2 months (range 2 - 23+).	Comment noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer	No comment.	Response noted.

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	Physicians, and Joint Collegiate Council for Oncology		
Questions for consultation *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*	Celgene	A phase 2 multicenter trial by Piekarz et al evaluated the efficacy and safety of romidepsin in 47 patients with PTCL who previously failed ≥1 PTCL therapies (Piekarz 2011). Of the 45 patients evaluable for response, the ORR was 38%. Median time to response was 1.8 months. Overall median DOR was 8.9 months (range, 2 to 74 months) and 29.7 months (range, 3 to 74 months) among complete responders (Piekarz 2011).	Comment noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	No comment.	Response noted.
Questions for consultation *Please answer any of the questions for consultation if not covered in the above sections. If appropriate,*	Celgene	No comment.	Response noted.
	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of	No comment.	Response noted.

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please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines).	Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology		
Additional comments on the draft scope.	Celgene	PTCL is a designated orphan disease. Available epidemiology data suggest that the patient numbers are likely to be low. Given the rarity of the condition, the availability of trial evidence, lack of clarity on comparator treatments, and the likely uncertainty around clinical and cost-effectiveness using conventional criteria, Celgene is of the opinion that romidepsin is not a suitable topic for a technology appraisal.	Comment noted. Following discussion at the scoping workshop it was agreed that the patient population was likely to be small but noted that other appraisals have looked at smaller populations and therefore it would also be appropriate to consider this topic. If this topic is formally referred to NICE as a technology appraisal, the reliability of the available evidence will be considered by the Committee when formulating its recommendations.

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	Lymphoma Association and Leukaemia CARE	No comment.	Response noted.
	National Cancer Research Institute Lymphoma Clinical Studies Group, Royal College of Physicians, Royal College of Radiologists, Association for Cancer Physicians, and Joint Collegiate Council for Oncology	No	Comment noted.

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

Bristol-Myers Squibb
Department of Health
Genzyme Therapeutics
Marie Curie Cancer Care
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing
Welsh Government

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Romidepsin for the treatment of relapsed or refractory peripheral T-cell lymphoma

Response to consultee and commentator comments on the provisional matrix of consultees and commentators

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.	Under relevant research groups the British National Lymphoma Investigation no longer exists.	Royal College of Physicians		Removed	This organisation has been removed.
2.	All lymphoma research at a national level is now carried out by the NCRI Lymphoma Clinical Studies Group	Royal College of Physicians		Noted	The National Cancer Research Institute is already listed on the matrix as a 'Relevant research group'.

3.	Remove Chinese National Healthy Living Centre from the matrix of consultees and commentators.	NICE Secretariat		Removed	The Chinese national Healthy Living Centre has requested only to be involved in Chinese related topics.
4.	Include the National Council of Palliative Care on the matrix of consultees and commentators under 'patient/carer groups'.	NICE Secretariat		Not included	This organisation's interests are not closely related to the appraisal topic. The National Council of Palliative Care has therefore not been included in the matrix of consultees and commentators under 'patient/carer groups'.
5.	Add the British Society of Blood and Bone Marrow Transplantation to the matrix of consultees and commentators under 'Professional group'.	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and meet the selection criteria to participate in this appraisal. The British Society of Blood and Bone Marrow Transplantation have been included in the matrix of consultees and commentators under 'professional groups'.

6.	Add NHS Blood and Transplant to the matrix of consultees and commentators under 'Professional groups'.	NICE Secretariat		Added	This organisation's interests are closely related to the appraisal topic and meet the selection criteria to participate in this appraisal. NHS Blood and Transplant have been included in the matrix of consultees and commentators under 'professional groups'.
7.	Add NHS Centre for Reviews and Dissemination and Centre for Health Economics – York as the Evidence Review Group for this appraisal	NICE Secretariat		Added	NHS Centre for Reviews and Dissemination and Centre for Health Economics – York have been selected as the Evidence Review Group for this appraisal,