National Institute for Health and Clinical Excellence

Multiple Technology Appraisal (MTA)

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer (including review of technology appraisal no. 91 and technology appraisal no. 222)

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Janssen-Cilag Ltd	Yes, accurate and complete	Thank you for your comment. No action required.
	MSD	No comments	No action required.
	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	Ovarian cancer should include cancers of the fallopian tube or primary peritoneal cancers. These are histologically similar to ovarian cancer, may be indistinguishable and are treated in the same way are ovarian cancer	Thank you for your comment. The background section of the scope has been amended to point out that fallopian tube and primary peritoneal cancer may be classified with ovarian cancer as a single group.
	Pharma Mar, S.A.	The background information is appropriate.	Thank you for your comment. No action required.
	Roche Products Limited	No comments	No action required.

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Background information (cont.)	Target Ovarian Cancer	**Background information** Paragraph 1: need to insert the word cancer after the word 'gynaecological' so that the sentence reads 'Ovarian cancer is a common gynaecological cancer'. Paragraph 3: Final sentence 'survival rate of less than 35%' - survival rate is 43% according to CRUK statistics and 36% according to the International Cancer Benchmarking Partnership project, so this sentence is incorrect. **The technologies section:** A short description of platinum chemotherapy would be useful here, given that many of the drugs covered in this topic will be appraised in the context of platinum chemotherapy.	Thank you for your comment. The background section has been amended so that the sentence reads 'Ovarian cancer is a common gynaecological cancer …' The epidemiology of the disease in the scope has been amended to reflect the figure from Cancer Research UK referred to in this comment. The background section has been amended to include a description of platinum chemotherapy.
The technology/ intervention	Janssen-Cilag Ltd	In the Intervention(s) section of the draft scope, for people with platinum-sensitive ovarian cancer, pegylated liposomal doxorubicin hydrochloride (Caelyx) is described as "monotherapy or in platinum-containing chemotherapy". For people with platinum-resistant or platinum-refractory ovarian cancer, Caelyx is described as "monotherapy". Please note that the SmPC for Caelyx does not specify whether Caelyx is to be used as monotherapy or in combination with other chemotherapy.	Thank you for your comment. The reference to monotherapy has been removed from the interventions for people with platinum-resistant or platinum-refractory ovarian cancer.
	MSD	No comments	No action required.
	NCRI Gynaecological Cancer Clinical Studies	The main inaccuracy of the technology / intervention, is that Caelyx (pegylated liposomal doxorubicin) [PLD] has not been available for nearly 12 months. The drug is manufactured by Johnson and Johnson and marketed in Europe by Janssen Cilag. The prediction at present is that Caelyx will not be available	Thank you for your comment. In its appraisals of health technologies, NICE is bound

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The technology/ intervention (cont.)	Group/RCP/RCR/ACP/JCCO	until 3rd quarter of 2013. This has provided significant challenges to the delivery of the NICE technology appraisal as it stands. In particular the clinical trial data testing Trabectedin in combination with PLD. Trabectedin is a promising new agent, also approved by NICE in the treatment of soft tissue sarcomas. The oncology community now has significant experience in its use, and in the majority of patients it is well tolerated. Level A evidence in relapsed ovarian cancer has demonstrated significant benefit, particularly in the population of women with 'partially-sensitive' relapse. A randomised phase III trial demonstrated an overall survival advantage and is postulated that some of the effect may be due to delaying the re-introduction of platinum (at subsequent progression). Trabectedin PLD is also useful in cases where allergy to carboplatin has occurred. This can be found in up to 20 % of patients treated at relapse. Densitisation regimens are complex and costly and trabectedin/ PLD offers and alternative in these cases. Both these factors make this drug advantageous in the treatment of relapsed ovarian cancer. In the absence of PLD for a further year, it would disadvantage our patients considerably if the use of trabectedin was stopped because of this. The second effect of the PLD shortage is that clinicians are not able to use the effective combination of carboplatin and PLD. Both drugs are individually approved for recurrent ovarian cancer. The CALYPSO trial evaluated the combination and compared it to carboplatin and paclitaxel. The PFS was non inferior- possibly superior and the toxicity less using carboplatin and PLD. Until the shortage of PLD arose the use of carboplatin and PLD in combination was extensively used in the 'platinum-sensitive' subgroup, particularly in women relapsing less than 12 months after prior platinum. The rapid uptake of this combination in many of regions of the UK (and in continental Europe) was at the expense of carboplatin and paclitaxel following publication of the CALYPSO data. The NCRI Gynae SubGroup has been pro-active in starting an audit of Myocet (Liposomal doxorubicin) use. This is the drug that we have been using in its place. However detailed pharmacokinetic comparisons between PLD and	by the UK marketing authorisation of the intervention under consideration. For trabectedin, the UK marketing authorisation states that trabectedin should be used in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of patients with relapsed platinum-sensitive ovarian cancer. NICE can only make recommendations relating to trabectedin within the context of its UK marketing authorisation. Myocet (liposomal doxorubicin hydrochloride) is not licensed for the treatment of recurrent ovarian cancer and therefore cannot be incorporated into this technology appraisal. In addition, the use of Myocet in people with recurrent ovarian cancer in the NHS is temporary and related to the current shortage of pegylated liposomal doxorubicin hydrochloride. When the supply of pegylated liposomal doxorubicin hydrochloride is

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The technology/ intervention (cont.)	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO (cont.)	Myocet, demonstrate that the latter is far closer to the parent compound, doxorubicin, in terms of area under the concentration time curve. Bevacizumab is being dealt with separately by NICE but would need to be factored into guidance that makes recommendations about the use of drugs in recurrent ovarian cancer Two drugs that are used in platinum-resistant disease should be considered. The first is platinum- although it seems counter intuitive to consider this drug in 'platinum-resistant' disease it should be noted from above that there are deficiencies in the definition of 'platinum-resistant' ovarian cancer. The drug can be quite active in this group of women, particularly when given in a 'dose-dense' setting ie weekly administration. However, much of the evidence for its activity is from phase II trials. The pharmaceutical industry has for obvious reasons not encouraged randomised comparisons of new drugs with eg dose-dense platinum. The academic community has been unsuccessful in obtaining funding for phase III trials in this setting as academic funders have thus far considered that the questions being addressed less interesting that exploration of more novel treatments. Nevertheless, there is consistency within the phase II literature that the combination of dose-dense platinum with eg etoposide or paclitaxel is very active in terms of response rate and PFS. Evidence for etoposide as an active single agent is less secure but phase II data do show benefit in terms of response rate and PFS. However, absorption of the oral drug is variable requiring careful monitoring as too high a dose can lead to significant myelosuppression and too little may be less effective.	restored, a switch is expected to be made. Bevacizumab cannot be included as an intervention in the scope because NICE can only make recommendations relating to the interventions covered by the remit of the appraisal. However, bevacizumab is a comparator for people with platinum-sensitive ovarian cancer. As part of its deliberations on clinical and cost effectiveness, the Committee would normally consider all relevant comparative evidence before making recommendations. The interventions and comparators relating to people with platinum-resistant or platinum-refractory ovarian cancer have been amended to include 'paclitaxel alone or in combination with platinum chemotherapy' and 'etoposide alone or in combination with platinum chemotherapy' respectively. This entails that paclitaxel in combination with platinum chemotherapy would

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The technology/ intervention (cont.)	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO (cont.)		be a comparator given that the comparators in the scope include the interventions under appraisal. Although the evidence for etoposide as a single agent may not be as compelling as for other interventions used in people with platinum-resistant or platinum-refractory ovarian cancer, etoposide is still a treatment option in the NHS for this subpopulation and therefore should be included as a comparator in the scope.
	Pharma Mar, S.A.	Yes, it is.	Thank you for your comment. No action required.
	Roche Products Limited	No comments	No action required.
	Target Ovarian Cancer	Yes	Thank you for your comment. No action required.
Population	Janssen-Cilag Ltd	Yes population is appropriate.	Thank you for your comment. No action required.
	MSD	No comments	No action required.

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Population (cont.)	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	The terms platinum 'sensitive ' and 'resistant' are convenient but need to be understood with some caution. They have become a useful guide for defining the probability of response to re-challenge with platinum (and are sometimes used to give a probability of response to non-platinum drugs). However, these are not categorical terms, so that patients relapsing 5 ½ months from previous platinum therapy may respond quite well to platinum re-challenge and with a similar effect to a women relapsing 6 ½ months after platinum. The definition of the terms arose from a retrospective analysis of a small amount of clinical experience at a time when platinum was the main drug that could be used on re-challenge. As a result, recommendations need to use the terms 'platinum-sensitive' and 'platinum-resistance' with some caution. Increasingly platinum, often in a weekly (dose-dense) schedule is offered to patients who are technically 'platinum-resistant' .The results measured by response rate or PFS are often very good. However, there is a paucity of data from randomised trials. The complexity of deciding in which order to give the various available treatments has not been addressed. This is probably because it is too complex to construct simple algorithms. Decisions around the next line of therapy to use in relapsed disease, may be clarified by a number of factors seen in earlier treatments; these include the development of anaphylaxis to carboplatin, or paclitaxel, or the persistence of moderate or severe peripheral neuropathy, the desire of a patient not to lose her hair again at a given point in time etc.	Thank you for your comment. The background section of the scope has been amended to highlight the caveat about defining categories for recurrent ovarian cancer based on the duration of response to initial platinum chemotherapy.
	Pharma Mar, S.A.	Yes, it is.	Thank you for your comment. No action required.
	Roche Products Limited	No comments	No action required.
	Target Ovarian Cancer	Yes	Thank you for your comment. No action required.

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Comparators	BMJ-Technology Assessment Group (BMJ-TAG)	Based on expert clinical advice the ERG considers that adding the following comparators could be of interest to this MTA: **Platinum-resistant or platinum-refractory:** • dose dense chemotherapy approaches such as: ○ weekly cisplatin and oral etoposide, ○ weekly carboplatin and weekly paclitaxel, and metronomic low dose oral cyclophosphamide.	The interventions and comparators relating to people with platinum-resistant or platinum-refractory ovarian cancer have been amended to include 'paclitaxel alone or in combination with platinum chemotherapy' and 'etoposide alone or in combination with platinum chemotherapy' respectively. This entails that paclitaxel in combination with platinum chemotherapy would be a comparator given that the comparators in the scope include the interventions under appraisal.
	Janssen-Cilag Ltd	Yes comparators are appropriate.	Thank you for your comment. No action required.
	MSD	No comments	No action required.

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Comparators (cont.)	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	We agree with comparators for platinum-sensitive relapse. As above, bevacizumab will need to be included or cross-referenced Platinum-resistant or platinum-refractory ovarian cancer – We agree with the interventions listed with two exceptions highlighted above. 1. dose-dense platinum should be considered in combination with paclitaxel or etoposide 2. We do not feel that oral etoposide should be used a valid single agent comparator It is well-recognised that ovarian cancer often responds for a considerable time to courses of chemotherapy. It is not unusual for women to receive 3 or 4 lines of treatment. The selection of women for multiple lines of treatment is complex and requires good clinical judgement; not all are suitable and it is difficult to construct algorithms specifying how many lines of treatment a woman should have. Looking at the UK survival statistics (and Eurocare), there has been some improvement in 1 year survival over the last decade [a partial reflection on first-line therapy] but much of the improvement in survival is probably due to the increase in availability of drugs at relapse, extending the life of women with ovarian cancer without increasing the cure rate for advanced disease. Mature results of randomised phase III trials also show increasing survival, again largely due to the results of treatment after first-line therapy Best supportive care is not an appropriate comparator in these patients. Patients who are fit and willing to undergo a further line of treatment would not submit themselves to a BSC control arm. However, we recognise that PROMs are increasingly important in this group of patients and are not adequately addressed in current studies. Studies are underway to improve the measurement of PROMs so that they can be incorporated into clinical trials	Thank you for your comment. Bevacizumab does not currently have a UK marketing authorisation for the treatment of platinum-resistant or platinum-refractory ovarian cancer. In addition, the evidence relating to the use of bevacizumab in this subpopulation is still emerging. In view of that, bevacizumab has not been included as a comparator for people with platinum-resistant or platinum-refractory ovarian cancer. Best supportive care is an option that some people with platinum-resistant or platinum-refractory ovarian cancer may wish to consider and therefore should be included in the scope. No action required.

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Comparators (cont.)	Pharma Mar, S.A.	Comparators selected are the standard treatments in the UK. So, they are appropriate.	Thank you for your comment. No action required.
	Roche Products Limited	Please see responses to the questions for consultation, below.	Thank you for your comment. No action required.
Outcomes	Janssen-Cilag Ltd	Yes outcome measures are appropriate.	Thank you for your comment. No action required.
	MSD	No comments	No action required.
	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	Yes but see comments above.	Thank you for your comment. No action required.
	Pharma Mar, S.A.	The outcome measures do capture the most important health related benefit for those with cancer	Thank you for your comment. No action required.
	Roche Products Limited	No comments	No action required.
	Target Ovarian Cancer	Yes	Thank you for your comment. No action required.
Economic analysis	Janssen-Cilag Ltd	No comment.	No action required.
	MSD	No comments	No action required.
	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	Don’t know	Thank you for your comment. No action required.

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Economic analysis (cont.)	Pharma Mar, S.A.	A life time horizon is appropriate for those with cancer.	Thank you for your comment. No action required.
	Roche Products Limited	No comments	No action required.
Equality and Diversity	Janssen-Cilag Ltd	No comment.	No action required.
	MSD	We are not aware of any equality issues related to this proposed appraisal.	Thank you for your comment. No action required.
	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	No equality issues	Thank you for your comment. No action required.
	Pharma Mar, S.A.	No comments on factors that may help eliminate inequality.	No action required.
	Roche Products Limited	No comments	No action required.
Innovation	MSD	No comments	No action required.
Other considerations	Janssen-Cilag Ltd	No comment.	No action required.
	MSD	No comments	No action required.

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Other considerations (cont.)	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	Consideration given to the 'order' of treatments is discussed above	Thank you for your comment. As per your comment on the 'Population', there is considerable complexity and variation in clinical practice in terms of specifying the order in which available treatments are given. This issue is beyond the remit of this appraisal and would normally be considered in the development of clinical guidelines. No action required.
	Roche Products Limited	No comments	No action required.
Questions for consultation	Janssen-Cilag Ltd	No comment.	No action required.
	MSD	*NICE intends to appraise vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of folate-receptor-positive platinum-resistant ovarian cancer as a single technology appraisal. Would it be more appropriate to include vintafolide in combination with pegylated liposomal doxorubicin hydrochloride in this review?* We believe that it would be most appropriate to appraise vintafolide through the STA process. *[confidential information removed / CIC]* It is expected that vintafolide will only be licensed for patients with *[confidential information removed / CIC]* platinum-resistant ovarian cancer, therefore the	Thank you for your comment. Vintafolide in combination with pegylated liposomal doxorubicin is expected to proceed as an STA. No action required.

Section	Consultees	Comments	Action
Questions for consultation (cont.)	MSD (cont.)	patient population to be appraised is different to that for all other therapies included in the MTA. Given the lack of trial data in the folate-receptor positive subgroup of patients for most of the therapies in the MTA, making a comparison between these and vintafolide would be challenging. If vintafolide were to be appraised as part of the review of this MTA an evidence submission would be required before marketing authorisation was granted, and conducting an appraisal without knowledge of the final licensed indication would be challenging. The need to understand the details of the regulatory approvals for the diagnostic agent and IV folic acid *[confidential information removed / CIC]* prior to providing an evidence submission for vintafolide will add to these difficulties. If the MTA was delayed to incorporate vintafolide this would result in a delay to publication of updated guidance for all products in the MTA. Treatment of recurrent ovarian cancer in UK clinical practice has changed greatly over recent years, and there is a need for updated guidance to ensure all patients receive the optimal therapies for their disease. In addition, incorporating vintafolide into an MTA would delay publication of guidance for vintafolide, as the MTA process is longer than for the STA. Vintafolide is an innovative product and there is a need for novel treatments for patients with platinum-resistant ovarian cancer, therefore it is important that guidance is issued to the NHS as close to the time of licence as possible.	
	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO	<u>*Questions for consultation*</u> *NICE intends to appraise vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of folate-receptor-positive platinum-resistant ovarian cancer as a single technology appraisal. Would it be more appropriate to include vintafolide in combination with pegylated liposomal doxorubicin hydrochloride in this review?* It is too early to assess vintafolide in this appraisal. The PROCEED trial – the pivotal study comparing EC145 + PLD v PLD is only just starting having been	Thank you for your comment. Vintafolide in combination with pegylated liposomal doxorubicin is expected to proceed as an STA. Bevacizumab does not

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Questions for consultation (cont.)	NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO (cont.)	delayed due to the worldwide shortage of PLD. *Have the most appropriate comparators been included in the scope?* • *Is bevacizumab a relevant comparator for people with platinum-resistant or platinum-refractory ovarian cancer? If so, in which regimens would it be used?* Yes: The data from the AURELIA trial need to be considered. This was highlighted in comments to NICE re bevacizumab. The emerging data using bevacizumab with chemotherapy in platinum-resistant disease appears as compelling as in platinum-sensitive disease • *Is it appropriate to include 'best supportive care' as a comparator for people with platinum-resistant or platinum-refractory ovarian cancer?* NO, as discussed above • *Are there any subgroups of people in whom the technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?* No- at the moment there is no biomarker. However, this is likely to change in the near future. Homologous recombination deficiency of DNA repair is a marker for sensitivity to PARP inhibitors and is found in patients with a BRCA mutation and in up to 50 % of patients with high grade serous ovarian cancer. A molecular test for HRD is not yet available *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* No equality issues with this appraisal.	currently have a UK marketing authorisation for the treatment of platinum-resistant or platinum-refractory ovarian cancer. In addition, the evidence relating to the use of bevacizumab in this subpopulation is still emerging. In view of that, bevacizumab has not been included as a comparator for people with platinum-resistant or platinum-refractory ovarian cancer. No action required.

Section	Consultees	Comments	Action
Questions for consultation (cont.)	Pharma Mar, S.A.	Potential sub-groups of interest may be: • Partial platinum sensitive patients • Those in which platinum therapy is not appropriate / suitable	Thank you for your comment. The scope has been amended to include 'subgroups according to duration of response to first-line platinum-based chemotherapy' and 'people who are not suitable for platinum-based chemotherapy' as subgroups.
	Roche Products Limited	Bevacizumab does not currently have a marketing authorisation for this indication (platinum-resistant or –refractory ovarian cancer in combination with paclitaxel, pegylated liposomoal docetaxel; or topotecan). *[confidential information removed / CIC]*	Thank you for your comment. No action required.

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Questions for consultation (cont.)	Target Ovarian Cancer	This MTA is an opportunity to revisit treatment options available to women with recurrent ovarian cancer and provide greater clarity on a topic which currently, can be very confusing for patients. **Question: Would it be more appropriate to include vintafolide in combination with pegylated liposomal doxorubicin hydrochloride in this review?** It is crucial that relevant technologies are made available as swiftly as possible as options are currently limited for women with ovarian cancer. Through this MTA trabectedin and gemcitabine could potentially become more accessible to patients. Inclusion of vintafolide in combination with pegylated liposomal doxorubicin hydrochloride in this review is not appropriate as this particular appraisal is only in the earliest phases and would most likely hold up publication of this MTA. **Is it appropriate to include 'best supportive care' as a comparator for people with platinum-resistant or platinum-refractory ovarian cancer? If so, how should 'best supportive care' be defined?** It is important that any decisions about treatment are discussed with patients, including best supportive care; this is a tricky area that both patients and clinicians find difficult to discuss.	Thank you for your comment. Vintafolide in combination with pegylated liposomal doxorubicin is expected to proceed as an STA. No action required.
Additional comments on the draft scope	Janssen-Cilag Ltd	No additional comments.	No action required.
	Roche Products Limited	No comments	No action required.

Section	Consultees	Comments	Action
Additional comments on the draft scope (cont.)	Target Ovarian Cancer	Section: Related NICE recommendations - Technology Appraisal in Preparation, 'Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer.' Earliest anticipated date of publication Apr 2013. This appraisal relates only to first-line treatment for ovarian cancer and to women with recurrent disease, it is therefore not relevant here.	Thank you for your comment. This appraisal has been removed from the 'Related NICE recommendations' section in the scope.

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

Department of Health
Eli Lilly and Company limited
GlaxoSmithKline UK Limited
Medicines and Healthcare products Regulatory Agency
Royal College of Nursing
Royal College of Pathologists