NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Name of technology: Trabectedin (Yondelis®)

Disease area: Yondelis is approved for the treatment of adult patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents; and in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) for the treatment of patients with relapsed platinum-sensitive ovarian cancer. This patient access scheme (PAS) applies to the relapsed ovarian cancer setting.

3.2 Please outline the rationale for developing the patient access scheme.

A PAS for trabectedin in patients with STS was considered and approved by NICE in 2009. PharmaMar propose that the approved PAS is extended to include all licensed indications, specifically women with relapsed platinum-sensitive ovarian cancer.

A multiple technology appraisal (MTA) has been scheduled (submissions were due in March 2013) examining topotecan, PLDH, paclitaxel, trabectedin and gemcitabine for advanced recurrent ovarian cancer. NICE are anticipated to consider the use of trabectedin in combination with PLDH in women with relapsed platinum sensitive ovarian cancer who are unsuitable for treatment with platinum-based chemotherapy because of allergy or intolerance due to residual toxicities, and patients who have partially platinum sensitive disease. Therefore in line with the recommendations sought from NICE, whilst the proposed PAS will be available for NHS patients in the entire licensed population, the numbers of patients likely to access the PAS described in Section 3.6 are based on these subgroups.

PharmaMar undertook a process of consultation in 2009 when the approved PAS was devised (detailed in Appendix A Section 5.1.2). Subsequently,

opinions were sought from existing scheme users in November 2012, to determine the acceptability of the current scheme and identify any enhancements which could reduce administrative burden associated with the scheme. Users confirmed that whilst their preference would be for a straight discount in the current financial climate, the PAS workload is manageable and the scheme is operationally robust (details discussed in Appendix A Section 5.1.3).

The reason why a simple discount has not been chosen to replace the existing PAS is two-fold:

1. NICE has recommended trabectedin as an option for patients with STS and this recommendation was based on the provision of the existing PAS. Following consultation and subsequent feedback from pharmacists using the PAS, it is both operationally robust and manageable and therefore, PharmaMar wish to preserve the PAS in this indication. The estimated number of patients per centre anticipated to access the scheme in the relapsed ovarian cancer indication will continue to be low and therefore initial concerns about cumulative administrative burden are unfounded.

2. Switching to a straight discount would mean that one discount would apply across both indications, which may result in PharmaMar receiving a higher discount in one indication over and above the amount deemed cost-effective by NICE. For example, if the trabectedin in relapsed platinum-sensitive ovarian cancer required a discount of 50% to become cost-effective, but in STS only required a discount of 25% to become cost-effective, then to achieve cost-effectiveness across both indications a discount of 50% would need to be applied. However, this amount would unfairly exceed the amount deemed cost-effective by NICE for the STS indication which is currently approved.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The scheme is financially based.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

Trabectedin in combination with PLDH is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer. The PAS will be available for NHS patients in the entire licensed population but it is expected that trabectedin will only apply to a subgroup of patients where it is sought to be recommended by NICE. The subgroup is referred to as patients with relapsed platinum sensitive ovarian cancer who are not suitable for treatment with platinum-based chemotherapy because of allergy or intolerance due to residual toxicities and patients who have partially platinum-sensitive disease (defined as a platinum free interval (PFI) between 6 and 12 months).

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The scheme will apply to patients who require more than 5 cycles of trabectedin plus PLDH. The rationale for selecting this scheme is to achieve acceptable cost-effectiveness outcomes. The expected costs to the NHS will be substantially reduced compared with previous estimates and will ensure patient access to treatment.

This scheme is based on and uses the methods of the PAS already in place for the use of trabectedin in patients with STS. Therefore pharmacists will be familiar with the scheme and the administrative burden of following the PAS for ovarian cancer is lessened. The criteria allow easy identification of eligible patients by monitoring the number of treatment cycles that patients receive through normal ordering procedures. There have been no issues in identifying eligible patients under the current PAS scheme for STS.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The population for England and Wales is estimated to be 56,839,104 for 2014 with females accounting for 51% resulting in 28,419,552.[1]

Incidence of ovarian cancer is 20.9 per 100,000 females. Therefore 28,419,552*20.9/100,000 = 6,058.[2]

Of this 6,058, 90% is epithelial ovarian cancer. Therefore 6,058*0.90 = 5,453.[3]

Of this 5,453, 75% are stages III/IV. Therefore 5,453*0.75 = 4,089.[4]

Of this 4,089, approximately 80% relapse. Therefore 4,089*0.80 = 3,272.[5,6]

This 3,272 is made up of approximately the following:

- 20% are platinum-resistant. Therefore 3,272*0.20 = 6556
- 80% are platinum-sensitive. Therefore 3,272*0.80 = 2,6176

As a result, the total incident patients for proposed scheme = 2,617

In consideration of the subgroup defined in Section 3.4 the patient numbers would be as follows:

Population 1: Patients who have partially platinum-sensitive disease (6-12 months): estimated as 30%.6 Of these it is assumed that 50% are unsuitable for platinum-based therapy.[4,5,6] Therefore 2,617*0.30*0.50 = 393

Population 2: Platinum-sensitive patients (>12 months) with an occurrence of hypersensitivity reactions during second line treatment: estimated as 20%.[7] Of these 47%7 have severe reactions and up to 25%[8] need to abandon platinum treatment (not amenable to desensitisation or other platinum based therapies). Therefore (2,617*0.70)*0.20*0.47*0.25 = 43

Population 3: Platinum-sensitive patients (>12 months) with an occurrence of neuropathy while treated with platinum based chemotherapy: estimated as 20%.[9] The probability of persistent neurological toxicity among platinum-sensitive patients (>12 months) and intolerant to be retreated with platinum at 1 year after end of therapy is 15%.[10] Therefore (2,617*0.70)*0.20*0.15 = 55

Total incident patients expected to use the scheme: 393+43+55 = 491.

Based on the OVA-301 study of 430 platinum-sensitive patients, 231 (54%) received greater than 5 cycles of trabectedin. Therefore the number of patients that are expected to go beyond the dose cap of 5 cycles are 491*0.54 = 265.

The distribution by numbers of cycles of trabectedin received based on the OVA-301 study, projected on to the 491 incident patients expected to use the scheme, is shown in Figure 1 and Table 1.

Figure 1: Expected number of cycles of trabectedin received for incident patients expected to use the PAS

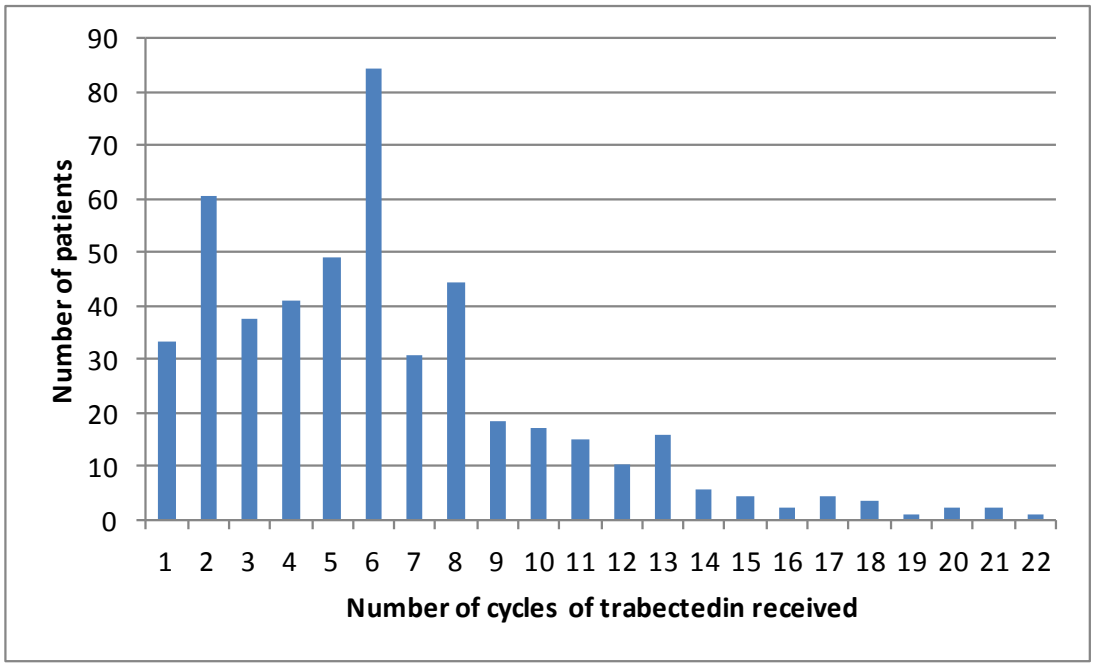


Table 1: Expected number of cycles of trabectedin received for incident patients expected to use the PAS

Number of cycles received	Number of patients (OVA-301)	Number of patients expected (incidence of 491)
1	29	33
2	53	61
3	33	38
4	36	41
5	43	49
6	74	84
7	27	31
8	39	45
9	16	18
10	15	17
11	13	15
12	9	10
13	14	16
14	5	6
15	4	5
16	2	2
17	4	5
18	3	3
19	1	1
20	2	2
21	2	2
22	1	1

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

Rebates will be calculated and paid in the following manner: participating NHS Hospital Trusts would order trabectedin in the same way as they would if there were no scheme in place except that they use order forms provided with the PAS administration pack. These are sent to PharmaMar's distributor (IDIS Ltd). Invoices will be issued as usual for orders received for patients on cycles 1–5. When an order is received for a patient on cycle 6 onwards, PharmaMar will authorise an appropriate rebate. Rebates will be in the form of either an adjustment to the invoice (free stock) or, if preferred, by credit note (the pharmacy will have indicated their preference when signing the trabectedin PAS agreement form). Credit notes will be sent on a monthly basis.

In addition, reconciliation can be completed retrospectively and rebate issued subsequently to ensure there is no delay to patient treatment.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The wording of the materials provided in Appendix A Section 5.1.1 have been standardised to be used with both indications.

The Chief Pharmacist (or authorised signatory) at hospitals wishing to participate in the PAS will sign an agreement form (contract) which details the terms and conditions of the scheme and allows pharmacies to choose their preferred rebate method. A small number of centres who have already signed an agreement for the PAS in the STS setting will be required to re-sign the agreement to cover both indications. PharmaMar will provide pharmacies with an updated administration pack containing materials enabling scheme management.

Participating NHS Hospital Trusts order trabectedin in the same way as they would if there were no scheme except that they use special order forms. For every treatment cycle administered to a patient eligible for trabectedin, a

pharmacist (PAS trained) completes a trabectedin order form and faxes a copy to PharmaMar's distributor (IDIS Ltd.). The form contains anonymised patient data (e.g. surname initials and date of birth (dd/mm)). On receiving an order, PharmaMar checks patient eligibility, notes the cycle number and, if the patient has already received five cycles, sends notification to the pharmacy indicating that the patient is now eligible for free of charge trabectedin. The pharmacy continues to claim every cycle for patients benefiting from trabectedin using the order form until completion of treatment. At the discretion of the institution, trabectedin would be rebated in the form of either an adjustment to the invoice (free stock) or by credit note. The pharmacy can use a patient cycle record to record each treatment cycle to monitor when a patient becomes eligible for free cycles, but this is entirely voluntary.

Staff grades involved in the tasks described in this section are listed in full by task in Section 4.5 Table 4.

As with the STS PAS, PharmaMar will work closely with hospital pharmacies to ensure the scheme's success: key pharmacy staff will be trained by PharmaMar Account Managers at each centre in the correct use of the PAS and a PAS binder (Administration pack) will be made available which will include a complete PAS guide for pharmacies and copies of the treatment cycle record and trabectedin order form documents.

A treatment cycle record can be used on a voluntary basis by pharmacies to keep a record of each patient's treatment history and for the purposes of audit. This is not mandatory and will not impact on the eligibility of patient receiving free cycles of treatment. It is, however, recommended that NHS institutions keep a copy of the trabectedin order form (available in paper and electronic formats) in case of reconciliation.

To ensure that the PAS works efficiently and that eligible patients continue to benefit from trabectedin plus PLDH treatment after cycle 5, occasional record reconciliation checks may be required. The objective would be to identify any discrepancies between records and, if required, rectify them. Reconciliation may be triggered for example by pharmacy request or if a spot-check is

initiated to ensure that the scheme is running smoothly under the terms of the PAS Agreement, and to identify areas for improvement. It is hoped that most queries can be resolved by phone. If a more formal check is needed, an Account Manager from PharmaMar will set up a meeting providing 60 days notice. For the meeting, an independent consultant will bring with them a full set of records (copies of orders, letters and other documents) that have been sent by the pharmacy, plus a summary report containing the numbers of active and past patients, numbers of rebates authorised and outstanding rebates due. During the meeting, these data will be compared with the pharmacy's information and discrepancies will be identified and documented using a checklist. After the meeting PharmaMar will send a copy of the completed checklist and a letter describing which actions will be taken to rectify discrepancies.

The scheme does not require additional assessment of patient status, tests or appointments.

The scheme will be monitored and implemented by PharmaMar, IDIS and the pharmacies of participating NHS Trusts as described by the flow charts in Section 3.9 (Figure 2 and Figure 3).

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Figure 2: Flow chart 1 - Overview of entire PAS operation

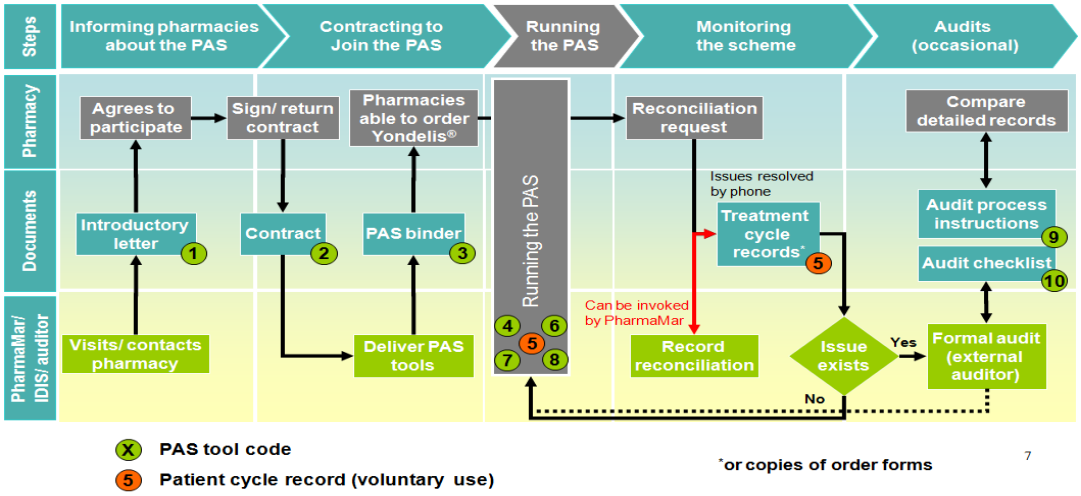


Figure 3: Flow chart 2 - Running the PAS

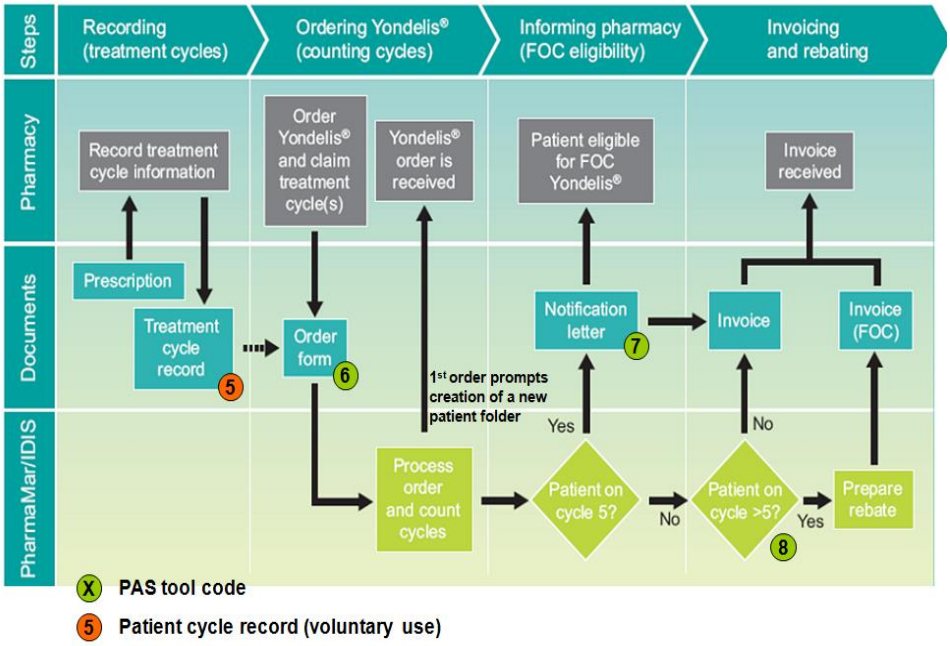


Table 2: PAS tool code documents

Tool	Description	Purpose
1	Introductory letter to hospitals/pharmacies	Sent to or given to hospital pharmacies to describe the scheme and provide information required for participation.
2	Agreement (contract with hospitals)	Delivered to hospital pharmacies with the introductory letter. Outlines the terms and conditions of the scheme and the pharmacy's rebate preference. Signed agreement triggers participation in the scheme.
3	PAS binder	Sent to hospital pharmacies. Contains materials to

	(Administration Pack)	help manage the PAS (i.e. 4, 5 and 6).
4	PAS Guide for pharmacies	Informs pharmacies of how the scheme works, what records to keep, how to make claims (via orders), what PharmaMar will do when order forms are received, and the audit process.
5	Treatment cycle record	Used on a voluntary basis by pharmacies to keep a record of each patient's treatment history. Paper and electronic versions are available.
6	Trabectedin order form	Used to order trabectedin for patients with indications covered by NICE guidance (currently STS). There are paper and electronic versions of this form. PharmaMar use these to maintain records of eligible treatment cycles. Pharmacists are encouraged to keep a copy of orders for their records (to help with reconciliation).
7	Notification of free drug eligibility	Letter/ email sent to the pharmacy to inform them that patient ABC (only surname initials) with date of birth dd/mm is eligible for free of charge trabectedin.
8	Rebate instructions to distributor	Used by PharmaMar to instruct their distributor to authorise supply of free drug (or alternatives) to pharmacies.
9	Audit process instructions	Audits can be performed occasionally to ensure the scheme is working as intended. This tool instructs auditors on how to audit a pharmacy.
10	Audit checklist	Checklist for use in the audit.

3.10 Please provide details of the duration of the scheme.

PharmaMar commit to continuing with the scheme until a subsequent applicable NICE Guidance is published on the NICE website following NICE review of trabectedin. In this case, PharmaMar will discuss and agree with Department of Health whether the PAS agreement is cancelled and a new PAS agreement must be signed or whether an amendment of the PAS agreement should be agreed between the parties. Or if the hospital breaches any material obligation established in the PAS agreement and such breach continues unabated for forty-five (45) days after written notice thereof from PharmaMar.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

No. The trabectedin PAS does not raise any issues when considered in the context of any protected characteristics such as sex, race, age or disability.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Table 3: Supporting documentation/tools for the trabectedin PAS

Tool	Description	Purpose
1	Introductory letter to hospitals/pharmacies	Sent to or given to hospital pharmacies to describe the scheme and provide information required for participation.
2	Agreement (contract with hospitals)	Delivered to hospital pharmacies with the introductory letter. Outlines the terms and conditions of the scheme and the pharmacy's rebate preference. Signed agreement triggers participation in the scheme.
3	PAS binder (Administration Pack)	Sent to hospital pharmacies. Contains materials to help manage the PAS (i.e. 4, 5 and 6).
4	PAS Guide for pharmacies	Informs pharmacies of how the scheme works, what records to keep, how to make claims (via orders), what PharmaMar will do when order forms are received, and the audit process.
5	Treatment cycle record	Used on a voluntary basis by pharmacies to keep a record of each patient's treatment history. Paper and electronic versions are available.
6	Trabectedin order form	Used to order trabectedin for patients with indications covered by NICE guidance (currently STS). There are paper and electronic versions of this form. PharmaMar use these to maintain records of eligible treatment cycles. Pharmacists are encouraged to keep a copy of orders for their records (to help with reconciliation).
7	Notification of free drug eligibility	Letter/ email sent to the pharmacy to inform them that patient ABC (only surname initials) with date of birth dd/mm is eligible for free of charge trabectedin.
8	Rebate instructions to distributor	Used by PharmaMar to instruct their distributor to authorise supply of free drug (or alternatives) to pharmacies.
9	Audit process instructions	Audits can be performed occasionally to ensure the scheme is working as intended. This tool instructs auditors on how to audit a pharmacy.
10	Audit checklist	Checklist for use in the audit.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The population to whom the scheme applies has been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal. As described in Section 3.4, the PAS will be available for NHS patients in the entire licensed population, that is, patients with relapsed platinum-sensitive ovarian cancer.

4.2 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

4.3 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the

assumptions that the Appraisal Committee considered most plausible.

The PAS has been incorporated into the cost-effectiveness analysis by recalculating the average number of treatment cycles of trabectedin the NHS would pay for based on the fact that after 5 cycles the NHS would bear no cost.

The base case model without a PAS calculated that on average a trabectedin plus PLDH patient would receive 6.86 cycles of trabectedin. Assuming that the NHS would only pay a maximum of 5 cycles, the NHS would pay for, on average, 4.28 cycles.

The number of cycles for which the NHS would pay for (4.28) was then used to calculate the acquisition cost of trabectedin with PAS. In addition, implementation/ administrative costs of the PAS were also included (see Section 4.5 Table 4 and Figure 4).

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The clinical effectiveness data used in the model does not change for the inclusion of the PAS and can be found in Section 7.10.1 of the main manufacturer/sponsor submission of evidence for the technology appraisal. As described in section 4.3, it should be noted that the average number of treatment cycles of trabectedin is costed as 4.28 with the PAS as opposed to 6.86 without the PAS.

4.5 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'

Table 4: Costs associated with the implementation and operation of the proposed PAS

	Calculation of cost	**Reference source**
Stock management	- Record individual supplies on local system – pharmacy technician/pharmacist: 1 NHS staff member Band 5 – Band 7 for 15 minutes = £3.84 - £5.61 - Stock management – pharmacy technician: 1 NHS staff member Band 5 for 10 minutes = £2.56 - Provide back-up information to Finance to invoice PCTs – pharmacist: 1 NHS staff member Band 8b for 10 minutes = £5.36	AFC 2011[11] PSSRU 2010[12]
Administration of claim forms	- Create patient treatment cycle record – pharmacy	AFC 2011[11] PSSRU 2010[12]

	technician/pharmacist: 1 NHS staff member Band 5 – Band 7 for 30 minutes = £7.68 - £11.22 - Complete order/claim form – pharmacist: 1 NHS staff member Band 7 for 10 minutes = £3.74 - Process free of charge supplies – pharmacy technician: 1 NHS staff member Band 5 for 15 minutes Band 5 = £3.84	
Staff training	- Create local systems – pharmacist: 1 NHS staff member Band 8a – Band 8b for 120 minutes = £54.48 - £64.32 - Staff training – pharmacy technician/pharmacist: 3 NHS staff members Band 5 – Band 8a for 20 minutes each = £5.12 - £9.08	AFC 2011[11] PSSRU 2010[12]
Tracking of supplies	- PCT tracking of patients and PCT audit of NHS trust invoice back-up data – medicines management: 1 NHS staff member Band 8b for 20 minutes = £10.72	AFC 2011[11] PSSRU 2010[12]
Other costs	- Review of agreement and authorisation: 1 NHS staff member Band 8C – Band 9 for 60 minutes = £38.16 - £55.44	AFC 2011[11] PSSRU 2010[12]
Other		
Total implementation and operation costs	NHS trust per patient monthly costs of the PAS £11.76 - £13.53 NHS trust per patient monthly costs of	AFC 2011[11] PSSRU 2010[12]

	claiming free of charge stock £15.26 - £18.80 NHS trust implementation and training £59.60 - £73.40 NHS trust scheme agreement £38.16 - £55.44 PCT per patient monthly costs of the PAS £10.72	

Based on the above costs and accounting for discounting using the exponential method with a 3.5% annual discount rate (see Section 7.7 of the main manufacturer/sponsor submission of evidence for the technology appraisal), the administration / implementation costs included in the model are shown in Figure 4.

Figure 4: PAS administration / implementation costs included in the model

PAS implementation costs	Annual cost	Years	Discounted cost
NHS trust costs of the PAS	£151.74	0.938	£140.07
NHS trust costs of claiming free of charge stock	£204.36	0.938	£188.64
NHS trust implementation and training	£66.50	-	£66.50
NHS trust scheme agreement	£46.80	-	£46.80
PCT costs of the PAS	£128.64	0.938	£118.74
TOTAL			**£560.74**

4.6 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

No additional costs will be incurred.

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

A suggested format is shown below (table 3).

Table 5: Base case cost effectiveness without PAS

	Trabectedin + PLDH (without PAS)	PLDH
Discounted intervention cost	£21,587	£8,044
Discounted administration cost	£2,274	£1,147
Discounted medical management cost	£19,650	£15,472
Discounted adverse event cost	£396	£146
Discounted total costs	£43,907	£24,809
Difference in discounted total costs	N/A	£19,098
LYG	3.72	2.91
LYG difference	N/A	0.81
Discounted QALYs	2.33	1.85
Discounted QALY difference	N/A	0.49
ICER	N/A	£39,306

LYG: life years gained; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio

Table 6: Base case cost effectiveness with PAS

	Trabectedin + PLDH (with PAS)	PLDH
Discounted intervention cost	£15,326	£8,044
Discounted administration cost	£2,274	£1,147
Discounted medical management cost	£19,650	£15,472
Discounted adverse event cost	£396	£146
Discounted PAS implementation cost	£561	£0
Discounted total costs	£38,206	£24,809
Difference in discounted total costs	N/A	£13,397
LYG	3.72	2.91
LYG difference	N/A	0.81
Discounted QALYs	2.33	1.85
Discounted QALY difference	N/A	0.49
ICER (£)	N/A	£27,573

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 7 shows the results of trabectedin plus PLDH compared to PLDH monotherapy without the PAS. Over a lifetime horizon a patient receiving trabectedin plus PLDH accrued 3.72 LYG and 2.33 QALYs at a cost of £43,907. Patients receiving PLDH monotherapy accrued 2.91 LYG and 1.85 QALYs at a cost of £24,809. The corresponding incremental cost per QALY was calculated as £39,306.

Table 8 shows the results of trabectedin plus PLDH compared to PLDH monotherapy with the PAS. Over a lifetime horizon a patient receiving trabectedin plus PLDH accrued 3.72 LYG and 2.33 QALYs at a cost of £38,206. Patients receiving PLDH monotherapy accrued 2.91 LYG and 1.85 QALYs at a cost of £24,809. The corresponding incremental cost per QALY was calculated as £27,573.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 7: Base-case incremental results without PAS

Technologies	Total			Incremental			ICER versus baseline (QALYs)	ICER incremental (QALYs)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
PLDH	£24,809	2.91	1.85	-	-	-	-	-
Trabectecdin + PLDH (without PAS)	£43,907	3.72	2.33	£19,098	0.81	0.49	£39,306	£39,306

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 8: Base-case incremental results with PAS

Technologies	Total			Incremental			ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs		
PLDH	£24,809	2.91	1.85	-	-	-	-	-
Trabectecdin + PLDH (with PAS)	£38,206	3.72	2.33	£13,397	0.81	0.49	£27,573	£27,573

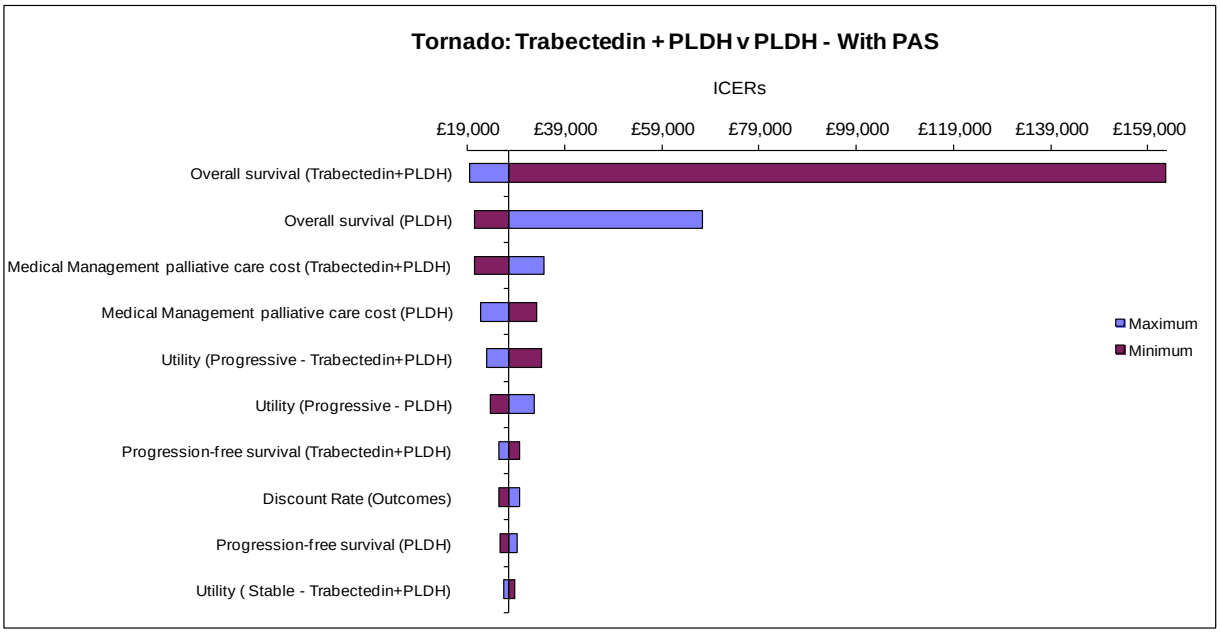
LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analysis was performed to assess the impact of uncertainty in model assumptions and parameters on the model results. Appendix C Section 5.1.13 shows the full results of the one-way sensitivity analysis (OWSA) and Figure 5 illustrates the ten most sensitive parameters in a Tornado diagram of trabectedin plus PLDH compared to PLDH monotherapy with the PAS. Please see Figure 7.6 in the main manufacturer/sponsor submission of evidence for the technology appraisal for OWSA without the PAS.

Figure 5: Tornado diagram depicting deterministic sensitivity analysis with PAS



The OWSA showed that results were sensitive to OS. The results were also fairly sensitive to medical management palliative care costs and utilities for progressive disease.

4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Table 9 shows the results of the probabilistic sensitivity analysis (PSA) are similar to that of the deterministic base case with the PAS shown in Table 8.

Table 9: Probabilistic incremental results with PAS

Technologies	Total			Incremental			ICER versus baseline (QALYs)	ICER incremental (QALYs)
	Costs	LYG	QALYs	Costs	LYG	QALYs		
PLDH	£24,931	2.91	1.86	-	-	-	-	-
Trabectecdin + PLDH (with PAS)	£38,206	3.72	2.35	£13,563	0.81	0.49	£27,761	£27,761

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

The PSA captures the overall uncertainty surrounding the ICER point estimate and is presented as an ICER plane in Figure 6 and CEAC in Figure 7. The ICER plane (Figure 6) shows that the majority of simulations were in the north-east quadrant where trabectedin plus PLDH is more costly and more effective than PLDH monotherapy. The CEAC showed that at a WTP of £20,000 per QALY and £30,000 per QALY, the probability that trabectedin plus PLDH remained cost-effective was 11% and 53%, respectively.

Figure 6: Incremental cost-effectiveness plane with PAS

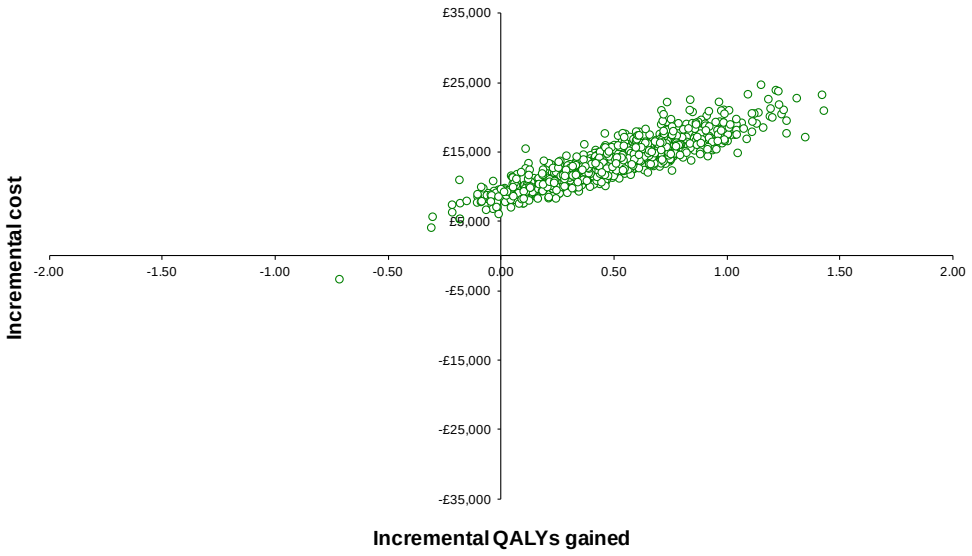
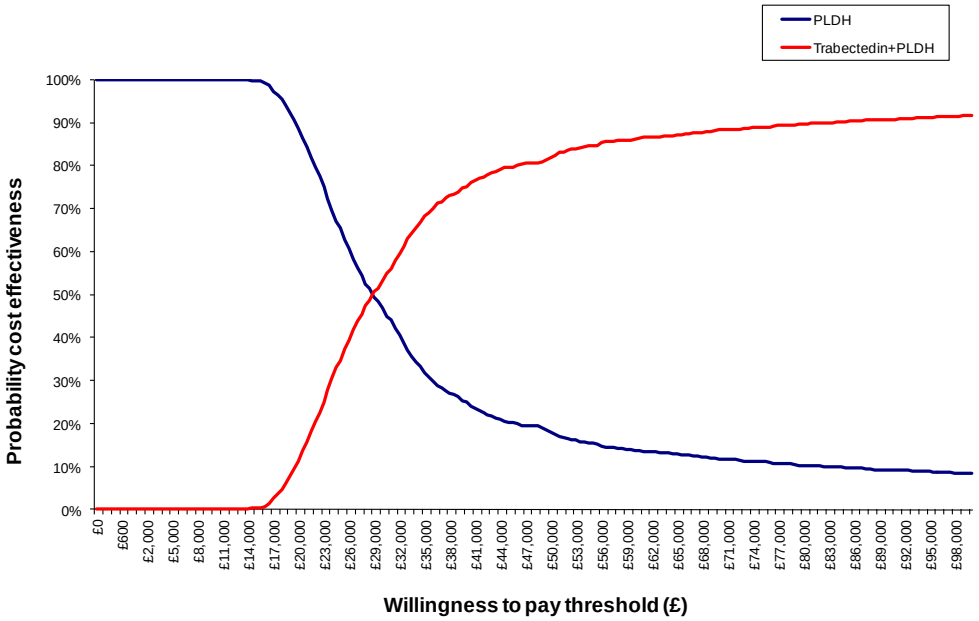


Figure 7: Cost-effectiveness acceptability curve with PAS



4.11 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Table 10 and Table 11 below present the results of the scenario analysis. Results were most sensitive to the adjustment of PFI as an explanatory variable. Although the selected survival distributions remained unchanged, the increase in the ICER was primarily due to an increase in OS from 34.97 to 41.44 in the PLDH arm, which was also associated with a significant increase in AIC from 472.7 to 504.7. The significant increases in AIC across the survival distributions suggested that not adjusting for PFI produced significantly worse fitting survival distributions. Results were also sensitive to considering alternative survival distributions for PFS and OS. The second best fitting distributions based on AIC and BIC were chosen; these were the Gompertz and Weibull, respectively. The ICER increased to over £35,000 when the more conservative (but worse fitting) Weibull distribution was used for OS as opposed to the Log-logistic. Goodness of fit was marginally worse when considering the Weibull (AIC=508.1) compared to the Log-logistic (AIC=508.0) distribution for trabectedin plus PLDH, and significantly worse when considering the Weibull (AIC=478.6) compared to the Log-logistic (AIC=472.7) distribution for PLDH monotherapy. Results were fairly insensitive to changes to utilities and adverse event assumptions.

Table 10: Sensitivity analysis with PFI adjustment and choosing different survival distributions with PAS

Scenario	Trabectedin plus PLDH (PFS)	PLDH monotherapy (PFS)	Trabectedin plus PLDH (OS)	PLDH monotherapy (OS)	ICER	Difference
Base case	Weibull AIC = 451.2	Weibull AIC = 380.9	Log-logistic AIC = 508.0	Log-logistic AIC = 472.7	£27,573	-
No PFI adjustment	Weibull AIC = 456.3	Weibull AIC = 385.8	Log-logistic AIC = 514.3	Log-logistic AIC = 504.7	£70,222	£42,649
Distribution 1	Gompertz AIC = 457.7	Gompertz AIC = 384.0	Log-logistic AIC = 508.0	Log-logistic AIC = 472.7	£27,572	-£1
Distribution 2	Weibull AIC = 451.2	Weibull AIC = 380.9	Weibull AIC = 508.1	Weibull AIC = 478.6	£35,485	£7,912
Distribution 3	Gompertz AIC = 457.7	Gompertz AIC = 384.0	Weibull AIC = 508.1	Weibull AIC = 478.6	£35,485	£7,912

Table 11: Scenario analysis with PAS

Scenario	Trabectedin + PLDH		PLDH		Incremental			
	Total Cost (£)	Total QALYs	Total Cost (£)	Total QALYs	Inc Cost (£)	Inc QALYs	ICER (£)	Difference (£)
Base Case	£38,206	2.33	£24,809	1.85	£13,397	0.49	£27,573	-
Utility weights								
Treatment and platinum-sensitive specific utilities	£38,206	2.46	£24,809	1.98	£13,397	0.48	£28,042	£469
Adverse events								
Neutropenia *Grade 3 (base case: £0, alternative scenario: £122.31) Grade 4 (base case: £0, alternative scenario: £2,346.49)*	£39,200	2.33	£25,094	1.85	£14,106	0.49	£29,033	£1,460
Neutropenic infection *Grade 3 and 4 (base case: £2,346.49, alternative scenario: £2,107.84)*	£38,205	2.33	£24,809	1.85	£13,396	0.49	£27,571	-£2
Neutropenic sepsis *Grade 3 and 4 (base case: £2,346.49, alternative scenario: £2,107.84)*	£38,205	2.33	£24,809	1.85	£13,396	0.49	£27,571	-£2

4.12 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Table 12: Sensitivity analysis with PAS

Scenario	Trabectedin + PLDH		PLDH		Incremental			
	Total Cost (£)	Total QALYs	Total Cost (£)	Total QALYs	Inc Cost (£)	Inc QALYs	ICER (£)	Difference (£)
Base Case (paid cycles = 4.28)	£38,206	2.33	£24,809	1.85	£13,397	0.49	£27,573	-
Assuming number of paid cycles = 5	£24,809	1.85	£39,964	2.33	£15,154	0.49	£31,190	£3,617
Assuming number of paid cycles = 4	£24,809	1.85	£37,533	2.33	£12,724	0.49	£26,189	-£1,384
Assuming number of paid cycles = 3	£24,809	1.85	£35,096	2.33	£10,286	0.49	£21,171	-£6,402

Impact of patient access scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Scenarios presented below are for parameters or assumptions results were sensitive to (see Section 4.9-4.12)

Table 13: Results showing the impact of patient access scheme on ICERs

	Trabectedin plus PLDH vs. PLDH ICER	
	Without PAS	**With PAS**
Scenario 1 (base-case)	£36,306	£27,573
Trabectedin plus PLDH OS + 20%	£25,854	£19,560
Trabectedin plus PLDH OS - 20%	£266,114	£162,675
PLDH OS + 20%	£106,120	£67,372
PLDH OS – 20%	£27,245	£20,388
No PFI adjustment	£109,892	£70,222
Distribution 1*	£39,320	£27,572
Distribution 2*	£52,589	£35,485
Distribution 3*	£52,611	£35,485

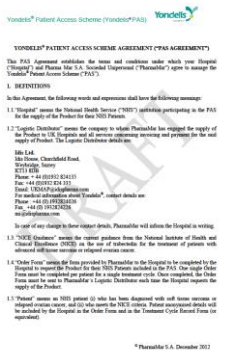
PAS: patient access scheme; OS: overall survival; PFI: platinum free interval
*See Table 11 for details of the distributions

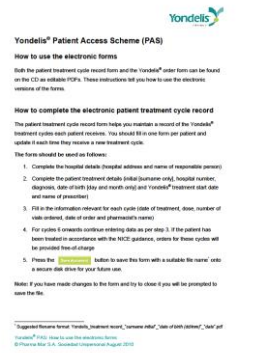
5 Appendices

5.1 Appendix A: Additional documents

5.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Table 14: Supporting documentation/tools for the trabectedin PAS

Tool	Description	Purpose	Document
1	Introductory letter to hospitals/pharmacies	Sent to or given to hospital pharmacies to describe the scheme and provide information required for participation.	N/A
2	Agreement (contract with hospitals)	Delivered to hospital pharmacies with the introductory letter. Outlines the terms and conditions of the scheme and the pharmacy's rebate preference. Signed agreement triggers participation in the scheme.	
3	PAS binder (Administration Pack)	Sent to hospital pharmacies. Contains materials to help manage the PAS (i.e. 4, 5 and 6).	N/A
4	PAS Guide for pharmacies	Informs pharmacies of how the scheme works, what records to keep, how to make claims (via orders), what PharmaMar will do when order forms are received, and the audit process.	Yondelis - Guide for pharmacists.pdf
5	Treatment cycle record	Used on a voluntary basis by pharmacies to keep a record of each patient's treatment history. Paper and electronic versions are available.	Yondelis Patient Treatment Cycle Rec
6	Trabectedin order form	Used to order trabectedin for patients with indications covered by NICE guidance (currently STS). There are paper and electronic versions of this form. PharmaMar use these to maintain records of	PAS ORDER FORM OC_STS March13.pdf

		eligible treatment cycles. Pharmacists are encouraged to keep a copy of orders for their records (to help with reconciliation).	 Yondelis **Yondelis® Patient Access Scheme (PAS)** **How to use the electronic forms** Both the patient treatment cycle record form and the Yondelis® order form can be found on the CD as editable PDFs. These instructions tell you how to use the electronic versions of the forms. **How to complete the electronic patient treatment cycle record** The patient treatment cycle record form helps you maintain a record of the Yondelis® treatment cycles each patient receives. You should fill in one form per patient and update it each time they receive a new treatment cycle. **The form should be used as follows:** 1. Complete the hospital details (hospital address and name of responsible person) 2. Complete the patient treatment details (initial (surname only), hospital number, diagnosis, date of birth (day and month only) and Yondelis® treatment start date and name of prescriber) 3. Fill in the information relevant for each cycle (date of treatment, dose, number of vials ordered, date of order and pharmacist's name) 4. For cycles 6 onwards continue entering data as per step 3. If the patient has been treated in accordance with the NICE guidance, orders for these cycles will be provided free-of-charge 5. Press the [illegible] button to save this form with a suitable file name' onto a secure data drive for your future use. Note: If you have made changes to the form and try to close it you will be prompted to save the file. Suggested filename format: 'Yondelis_treatment record_"surname initial"_"date of birth (dd/mm)"_"date".pdf' Yondelis® PAS: How to use the electronic forms © Pharma Mar S.A. Sociedad Unipersonal August 2010
7	Notification of free drug eligibility	Letter/ email sent to the pharmacy to inform them that patient ABC (only surname initials) with date of birth dd/mm is eligible for free of charge trabectedin.	Pharma Mar 19 September 2012 Mr Tim McCarthy Drug Resource Manager The Royal Marsden NHS Foundation Trust Downs Road Sutton SM2 5PT Dear Mr McCarthy **Yondelis® Patient Access Scheme (PAS)** Thank you for completing the PAS Order Forms for each cycle of treatment for your patient 5 (DoB: 07/06). Pharmamar would like to confirm that your patient is eligible for free-of-charge Yondelis® from treatment cycle 6 onwards. Yours sincerely AHMS Dillon Regional Unit Head PharmaMar, c/o Quintiles [illegible] Phone: [illegible] E-mail: [illegible]
8	Rebate instructions to distributor	Used by PharmaMar to instruct their distributor to authorise supply of free drug (or alternatives) to pharmacies.	N/A
9	Audit process instructions	Audits can be performed occasionally to ensure the scheme is working as intended. This tool instructs auditors on how to audit a pharmacy.	N/A
10	Audit checklist	Checklist for use in the audit.	N/A

5.1.2 NHS Consultation (2009)

The PAS concept and the patient cycle record and treatment cycle claim forms for the STS indication were tested in September 2009 with the following oncology pharmacists:

- Nicola Stoner - Lead Oncology Pharmacist, Thames Valley Cancer Network

- Ian Costello (Chief Pharmacist) and Suraya Quadir (Senior Pharmacist/ Pharmacy Manager), Royal Marsden Hospital

- Andrew Stanley – Senior network Advisor, pan Birmingham Network, BOPA board member

- Lesley Ryan – BOPA executive member

The findings were that the process is clear and simple to manage. Similarities with existing schemes were considered beneficial, however, compared to some other schemes, the trabectedin PAS was considered to have a lower administrative burden. The pharmacists thought that the forms are simple to use, contain relevant information and ask sensible questions. Flexibility in rebate options (free-stock, credit notes or cash repayments) was thought to be useful.

All interviewees stated the scheme was acceptable and similar to others already approved by the Department of Health. After the research the treatment cycle form was replaced with the order form which links cycle claims and ordering and further reduces the administration burden to pharmacies.

PharmaMar is confident that the relapsed platinum-sensitive ovarian cancer PAS will be successful because the STS scheme is already in place and has demonstrated that it is feasible, manageable and accepted by hospital pharmacies.

5.1.3 NHS Consultation (2012)

- Rena Chauhan – Senior Cancer Services Pharmacist, Nottingham University Hospitals NHS Trust

- Lyn Williams – Aseptic Pharmacy Manager, The Clatterbridge Cancer Centre NHS Foundation Trust

Existing trabectedin STS PAS users were contacted directly to establish current levels of satisfaction with the running of the existing PAS. Respondents were asked directly to describe any improvements that could be made to the scheme. Ratification of estimates of administrative burden was also completed (as shown in Section 4.5 Table 4) during consultation.

Whilst they acknowledged that a discount scheme is always the preferred approach, overall, the respondents expressed satisfaction with the PAS in its current format. Both pharmacists administer the existing PAS for less than 10 patients per year and confirmed that the workload is manageable and that the scheme is operationally robust.

Both pharmacists identified that being able to hold a small amount of trabectedin in stock and restrospectively reconcile PAS orders with patient issues ensures that the PAS runs effectively. PharmaMar confirm that this continues to be allowed within the terms and conditions of the trabectedin PAS. Processes have also been put in place in one centre to allow out-sourcing of chemotherapy reconstitution services.

Appendix B: Details of outcome-based schemes

5.1.4 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.1.5 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.1.6 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

5.1.7 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.1.8 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.1.9 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.1.10 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.1.11 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not applicable.

5.1.12 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

Appendix C: Sensitivity analysis

5.1.13 Sensitivity analysis

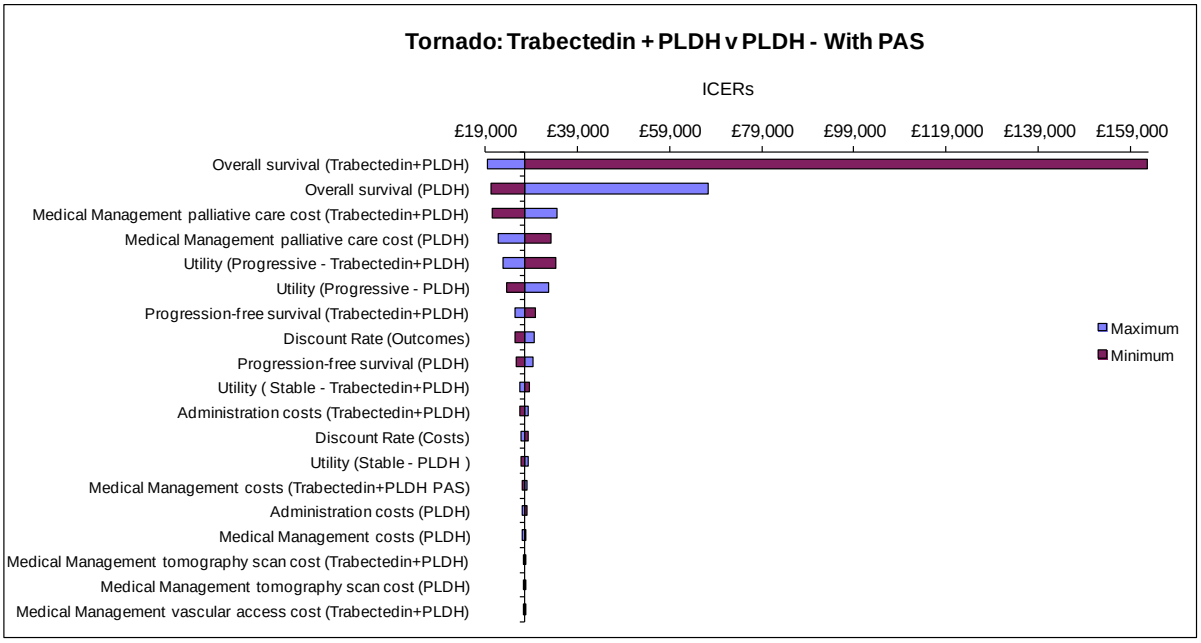
Table 15: One-way sensitivity analysis with PAS

Deterministic Sensitivity Analysis	Parameter value	Trabectedin plus PLDH		PLDH		Incremental			
		Total Cost (£)	Total QALYs	Total Cost (£)	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£)	Difference (£)
Base Case		£38,206	2.33	£24,809	1.85	£13,397	0.49	£27,573	-
Cost discount rate	6%	£37,205	2.33	£24,167	1.85	£13,039	0.49	£26,836	-£737
	1%	£39,293	2.33	£25,498	1.85	£13,795	0.49	£28,393	£820
Outcomes discount rate	6%	£38,206	2.24	£24,809	1.79	£13,397	0.45	£29,781	£2,208
	1%	£38,206	2.44	£24,809	1.91	£13,397	0.53	£25,477	-£2,096
Overall survival (Trabectedin plus PLDH)	+20%	£42,525	2.75	£24,809	1.85	£17,716	0.91	£19,560	-£8,013
	-20%	£33,775	1.90	£24,809	1.85	£8,965	0.06	£162,675	£135,102
Overall survival (PLDH)	+20%	£38,206	2.33	£28,294	2.19	£9,912	0.15	£67,372	£39,799
	-20%	£38,206	2.33	£21,254	1.50	£16,952	0.83	£20,388	-£7,185
Progression-free survival (Trabectedin plus PLDH)	+20%	£37,484	2.34	£24,809	1.85	£12,675	0.50	£25,434	-£2,139
	-20%	£38,933	2.32	£24,809	1.85	£14,123	0.47	£29,841	£2,268
Progression-free survival (PLDH)	+20%	£38,206	2.33	£24,210	1.86	£13,996	0.48	£29,366	£1,793
	-20%	£38,206	2.33	£25,411	1.84	£12,795	0.50	£25,840	-£1,733
Utility (Stable – Trabectedin plus PLDH)*	UCI = 0.738	£38,206	2.35	£24,809	1.85	£13,397	0.50	£26,583	-£990
	LCI = 0.698	£38,206	2.31	£24,809	1.85	£13,397	0.47	£28,640	£1,067
Utility (Stable - PLDH)*	UCI = 0.738	£38,206	2.33	£24,809	1.86	£13,397	0.47	£28,351	£778
	LCI = 0.698	£38,206	2.33	£24,809	1.83	£13,397	0.50	£26,837	-£736
Utility (Progressive – Trabectedin plus PLDH)*	UCI = 0.686	£38,206	2.43	£24,809	1.85	£13,397	0.58	£23,032	-£4,541
	LCI = 0.612	£38,206	2.24	£24,809	1.85	£13,397	0.39	£34,344	£6,771

Utility (Progressive - PLDH)*	UCI = 0.686	£38,206	2.33	£24,809	1.92	£13,397	0.41	£32,841	£5,268
	LCI = 0.612	£38,206	2.33	£24,809	1.77	£13,397	0.56	£23,762	-£3,811
Administration costs (Trabectedin plus PLDH)	+20%	£38,661	2.33	£24,809	1.85	£13,852	0.49	£28,509	£936
	-20%	£37,751	2.33	£24,809	1.85	£12,942	0.49	£26,637	-£936
Administration costs (PLDH)	+20%	£38,206	2.33	£25,039	1.85	£13,167	0.49	£27,101	-£472
	-20%	£38,206	2.33	£24,580	1.85	£13,626	0.49	£28,045	£472
Medical Management outpatient cost (Trabectedin plus PLDH)	+20%	£38,475	2.33	£24,809	1.85	£13,666	0.49	£28,126	£553
	-20%	£37,937	2.33	£24,809	1.85	£13,128	0.49	£27,020	-£553
Medical Management outpatient cost (PLDH)	+20%	£38,206	2.33	£25,007	1.85	£13,199	0.49	£27,166	-£407
	-20%	£38,206	2.33	£24,611	1.85	£13,595	0.49	£27,981	£408
Medical Management tomography scan cost (Trabectedin plus PLDH)	+20%	£38,345	2.33	£24,809	1.85	£13,535	0.49	£27,858	£285
	-20%	£38,068	2.33	£24,809	1.85	£13,258	0.49	£27,288	-£285
Medical Management tomography scan cost (PLDH)	+20%	£38,206	2.33	£24,911	1.85	£13,295	0.49	£27,363	-£210
	-20%	£38,206	2.33	£24,707	1.85	£13,499	0.49	£27,783	£210
Medical Management palliative care cost (Trabectedin plus PLDH)	+20%	£41,641	2.33	£24,809	1.85	£16,832	0.49	£34,643	£7,070
	-20%	£34,771	2.33	£24,809	1.85	£9,962	0.49	£20,504	-£7,069
Medical Management palliative care cost (PLDH)	+20%	£38,206	2.33	£27,604	1.85	£10,602	0.49	£21,821	-£5,752
	-20%	£38,206	2.33	£22,015	1.85	£16,191	0.49	£33,325	£5,752
Medical Management vascular access cost (Trabectedin plus PLDH)	+20%	£38,294	2.33	£24,809	1.85	£13,485	0.49	£27,754	£181
	-20%	£38,118	2.33	£24,809	1.85	£13,309	0.49	£27,392	-£181

*UCI and LCI calculated based on 95% lower and upper confidence intervals of the respective Beta distributions used in the PSA

Figure 8: Tornado diagram depicting deterministic sensitivity analysis with PAS



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