NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia

Patient Access Scheme Submission

21st October 2014

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.

The patient access scheme (PAS) applies to the purchase of obinutuzumab (Gazyvaro). The PAS proposed covers all populations for which obinutuzumab has an EMA marketing authorization.

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

The scheme is designed to bring the cost of obinutuzumab in combination with chlorambucil down to a level at which it can be considered a cost-effective use of NHS resources in patients unsuitable for treatment with a bendamustine based regimen.

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

The PAS is a simple discount (a [redacted]% discount below the current list price of obinutuzumab).

This equates to a net price of £[redacted] per 1000mg vial (compared to a list price of £3312).

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?

The PAS is a simple discount applied at the point of invoice. The PAS will apply to all patients for whom obinutuzumab is indicated.

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.

See above. The scheme is not dependent upon any criteria and is simply applied at the point of purchase.

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

The scheme will apply to all patients for whom obinutuzumab is indicated.

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

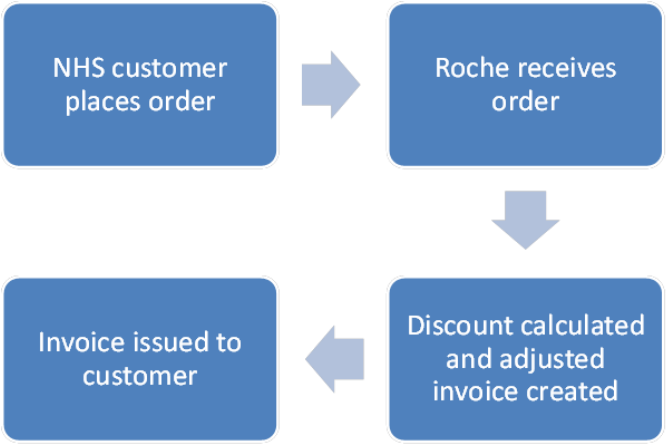
The discount will be applied at the point of invoice.

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 discount will be applied at the point of invoice.

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

See below:



3.10 Please provide details of the duration of the scheme.

The scheme will remain in place until the publication of any revised NICE guidance relating to obinutuzumab. After any review, the scheme may be withdrawn or modified or carried on in its current form depending upon the outcome of the re-review.

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?

There are no equity or equality issues relating to the scheme taking into account current legislation.

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.

Not applicable.

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.

Cost effectiveness

3.14 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 PAS applies to the population considered in our primary evidence submission.

3.15 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.

3.16 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 applied by reducing the price of obinutuzumab to [redacted]% below the list price stated in the primary evidence submission.

This equates to a net price of £[redacted] per 1000mg vial (compared to a list price of £3312).

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

As the PAS is a simple discount the clinical effectiveness data provided in the primary evidence submission is unaffected by the proposal.

3.18 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'

The PAS is a simple discount introduced at the point of invoicing. It is therefore not subject to operational or implementation costs.

3.19 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.

Not applicable.

Summary results

Base-case analysis

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

- the results for the intervention without the patient access scheme

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

- the results for the intervention with the patient access scheme.

The original Roche base case submitted is shown in Table 1(without PAS) Table 2 (with PAS).

The base case does not incorporate any of the Appraisal Committees preferred parameter values which were identified at ACD. These values have a significant effect on the ICERs.

We have supplied an appendix to the ACD which provides an updated base case incorporating the Committees preferred values and also a factually accuracy correction to the valuation of neutropenia. We also present a sensitivity analysis resulting from additional evidence which has become publically available on PFS utility values which we believe may alter the Committees preferred value for this parameter.

Table 1: Submitted base-case cost-effectiveness results without PAS

	G-Clb	**R-Benda**	**R-Clb**	**Benda**	**Clb**
Technology acquisition cost	£23,157	£15,243	£9,545	£4,745	£286
Other costs	£11,732	£11,972	£10,457	£10,812	£7,735
Total costs	£34,888	£27,215	£20,002	£15,557	£8,020
Difference in total costs	-	£7,673	£14,886	£19,331	£26,868
LYG	5.79	5.42	5.08	5.04	4.60
LYG difference	-	0.36	0.70	0.74	1.19
QALYs	4.03	3.65	3.33	3.30	2.92
QALY difference	-	0.38	0.70	0.73	1.11
ICER	-	£20,076	£21,275	£26,463	£24,256

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER: Incremental Cost-effectiveness Ratio; LYG: Life Years Gained; QALY(s): Quality-adjusted Life Year(s); R: Rituximab

Table 2: Submitted base-case cost-effectiveness results with PAS

	G-Clb	R-Benda	R-Clb	Benda	Clb
Technology acquisition cost	£[redacted]	£15,241	£9,545	£4,745	£286
Other costs	£11,732	£11,972	£10,457	£10,812	£7,735
Total costs	£[redacted]	£27,213	£20,002	£15,557	£8,020
Difference in total costs	-	£[redacted]	£[redacted]	£[redacted]	£[redacted]
LYG	5.79	5.42	5.08	5.04	4.60
LYG difference	-	0.37	0.70	0.74	1.19
QALYs	4.03	3.64	3.33	3.30	2.92
QALY difference	-	0.39	0.70	0.73	1.11
ICER	-	£[redacted]	£[redacted]	£[redacted]	£[redacted]

Benda: Bendamustine; Clb: Chlorambucil; G: Obinutuzumab; ICER: Incremental Cost-effectiveness Ratio; LYG: Life Years Gained; QALY(s): Quality-adjusted Life Year(s); R: Rituximab

3.21 Please present in separate tables the incremental results as follows.

- 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.

As defined in section 3.2 we present

- base case results as per Roche original submission - (Table 3) without a PAS, (Table 4) with PAS

Table 3: Base-case incremental results as per Roche submission – without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Clb	£8,020	4.60	2.92				
Benda	£15,557	5.04	3.30	£7,536	0.45	0.38	£19,983
R-Clb	£20,002	5.08	3.33	£4,445	0.04	0.03	£144,269
RBenda	£27,215	5.42	3.65	£7,213	0.34	0.32	£22,718
G-Clb	£34,888	5.79	4.03	£7,673	0.36	0.38	£20,076

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

Table 4: Base-case incremental results as per Roche submission with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Clb	£8,020	4.60	2.92				
Benda	£15,557	5.04	3.30	£7,536	0.45	0.38	£19,983
RClb	£20,002	5.08	3.33	£4,445	0.04	0.03	£144,269
RBenda	£27,213	5.42	3.65	£7,210	0.34	0.32	£22,967
GClb	£[redacted]	5.79	4.03	£[redacted]	0.36	0.38	£[redacted]

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

Sensitivity analyses

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

The sensitivity analysis is in line with that carried out by the ERG and is focused on the utility value applied to patients in PFS whilst off treatment. In their ERG report the ERG state that "We can identify no other sensitivity analysis for which there is another credible value and for which the ICER changes substantially" – as a result this is the focus of the sensitivity analysis presented.

Table 5: Base case (with PAS): parameters varied in deterministic sensitivity analysis

			GClb versus			
Variable	**Base Case Value**	**Sensitivity Analysis Value**	**Clb**	**Benda**	**RClb**	**RBenda**
Base Case			**£[redacted]**	**£[redacted]**	**£[redacted]**	**£[redacted]**
PFS off treatment	0.82	0.76	£[redacted]	£[redacted]	£[redacted]	£[redacted]

<u>Budget Impact of NICE approval of obinutuzumab</u>

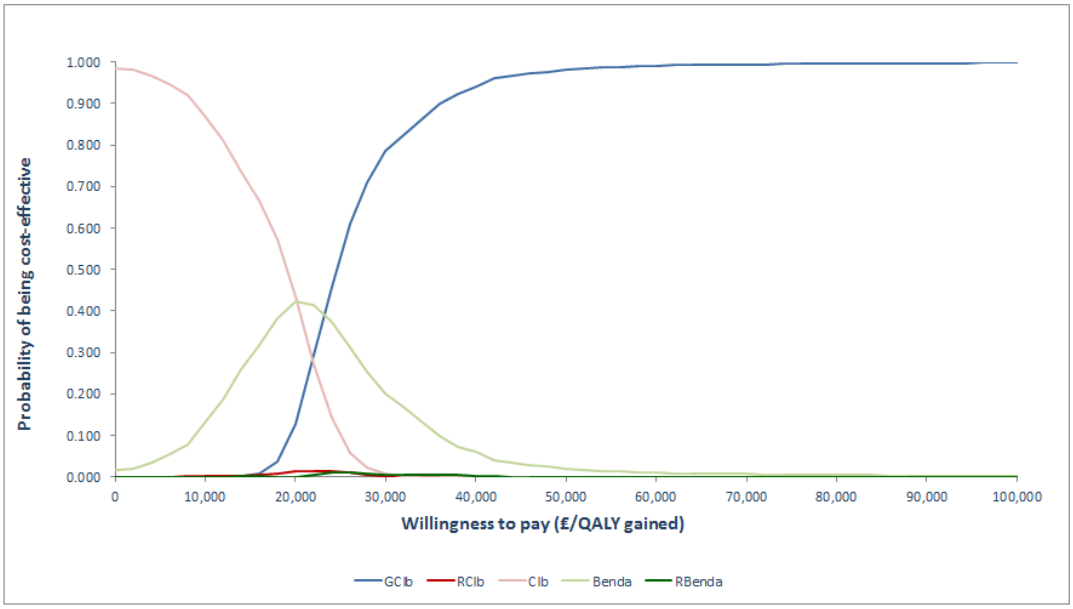
Table 6: Budget Impact of NICE approval (with [redacted]% discount)

Year	1	2	3	4	5
Mean drug cost	£[redacted]	£[redacted]	£[redacted]	£[redacted]	£[redacted]
Mean non-drug cost	£3,639,580	£4,877,038	£6,126,779	£7,388,895	£8,663,480
Mean total cost	**£[redacted]**	**£[redacted]**	**£[redacted]**	**£[redacted]**	**£[redacted]**

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

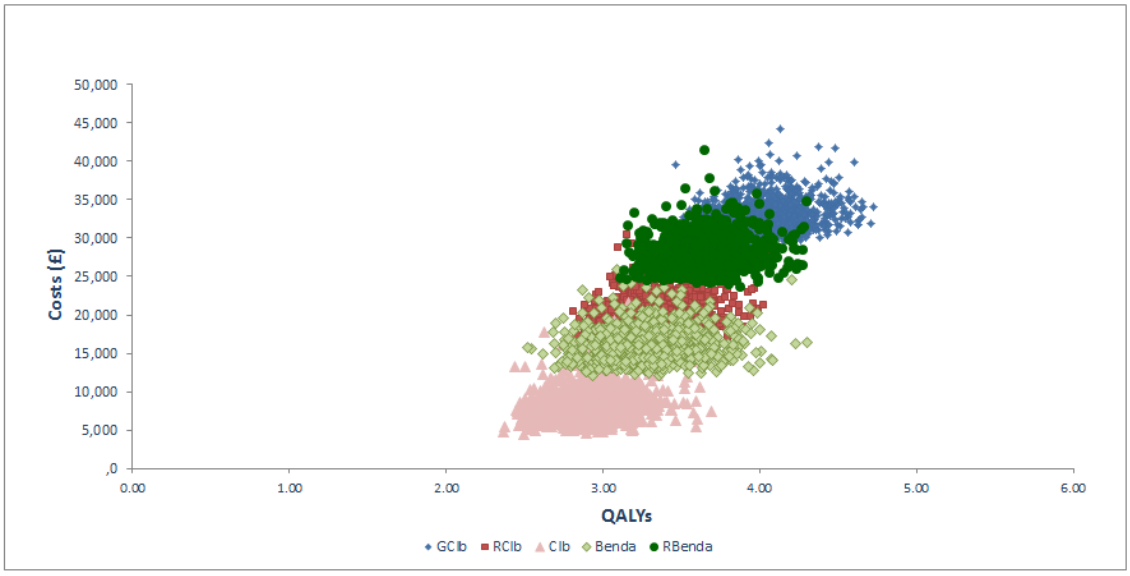
Below CEAC and scatter plots are presented for the base case including PAS.

Figure 1: CEAC Base case (with PAS) all comparators



In this population the probability of obinutuzumab being considered a cost-effective use of NHS resources is 74.4% at £30,000/QALY gained.

Figure 2: Scatter plot - Base case (with PAS) all comparators



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

See above.

3.25 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.

Not applicable.

Impact of patient access scheme on ICERs

3.26 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.

See above.

4 Appendices

4.1 Appendix A: Additional documents

4.1.1 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.

Not applicable.