NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation positive malignant melanoma

Patient Access Scheme Submission

13th April 2012

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 vemurafenib (Zelboraf). The PAS proposed covers all populations for which vemurafenib 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 vemurafenib down to a level at which it can be considered cost-effective.

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 vemurafenib).

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 vemurafenib 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 vemurafenib is indicated.

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

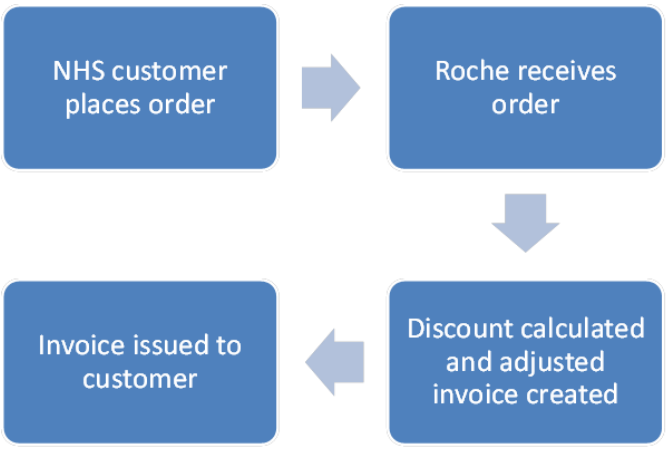
The discount will be applied at the point of invoice.

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 vemurafenib. 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 vemurafenib to [redacted] % below the list price stated in the primary evidence submission.

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

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

Table 1: Base-case cost-effectiveness results without PAS

	Vemurafenib	Dacarbazine
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	£94,267	

Table 2: Base-case cost-effectiveness results with [redacted] % discount

	Vemurafenib	Dacarbazine
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	£56,410	

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.

Table 3: Base-case incremental results – without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Dacarbazine	[redacted]	[redacted]	[redacted]					
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£94,267	£94,267

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

Table 4: Base-case incremental results – with [redacted] % discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Dacarbazine	[redacted]	[redacted]	[redacted]					
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,410	£56,410

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

If it is believed that the current discount rate of 3.5% for health outcomes is excessively high (as suggested by Claxton et al. 2011) then the ICERs presented above will be an over-estimate of the true ICER of utilising vemurafenib.

For example if a discount rate of 1.5% rather than 3.5% were to be utilised for health the ICER estimated would fall to **£48,249**.

Furthermore if the discount rates previously utilised by NICE were to be applied in the model (6% for costs and 1.5% for health) the ICER associated with vemurafenib falls to **£46,769**.

If it is assumed that a patient diagnosed with terminal cancer values each additional day of life at a utility value of 1 then the base-case ICER falls to **£38,831**.

If this is combined with discounting approach previously employed by NICE the ICER falls to **£31,488**.

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.

Table 5: Parameters varied in deterministic sensitivity analysis (with PAS)

Parameter	Base-Case Value	Low Value	High Value		Base-Case ICER	Low Value ICER	High Value ICER
Transition Probabilities							
Monthly hazard of disease progression after month 9 (vemurafenib) – note: KM used before this point in time.	0.2087	-10%	+10%		£56,410	£57,110	£55,830
Monthly hazard of disease progression after month 7 (dacarbazine) - note: KM used before this point in time.	0.2437	-10%	+10%		£56,410	£56,443	£56,382

Monthly hazard of death between month 9 and month 14 (vemurafenib). note: KM used before this point in time.	0.0761	-10%	+10%	£56,410	£52,465	£60,936
Monthly hazard of death between month 9 and month 14 (dacarbazine). note: KM used before this point in time.	0.0855	-10%	+10%	£56,410	£60,084	£53,328
Monthly hazard of death between month 14 and month 23 (both arms)	0.0658	-10%	+10%	£56,410	£54,552	£58,301

Monthly hazard of death between month 23 and month 35 (both arms)	0.0328	-10%	+10%		£56,410	£55,294	£57,534
Monthly hazard of death between month 35 and month 46 (both arms)	0.0141	-10%	+10%		£56,410	£56,002	£56,818
Monthly hazard of death from month 46 onwards - note: model includes IF statement linked to age/gender adjusted background mortality so that highest rate of this figure and background mortality is used in	0.001905	-50%	+50%		£56,410	£54,306	£58,871

model						
Utility Values						
Progression Free Survival (Response)	0.85	0.833 (Lower confidence interval)	0.867 (Upper confidence interval)	£56,410	£56,862	£55,947
Progression Free Survival (Stable Disease)	0.77	0.755 (Lower confidence interval)	0.785 (Upper confidence interval)	£56,410	£56,487	£56,331
Progressed Disease	0.59	0.578 (Lower confidence interval)	0.602 (Upper confidence interval)	£56,410	£57,024	£55,821
Skin reaction (Rash)	-0.03	-0.0297 (Lower confidence	-0.0303 (Upper confidence	£56,410	£56,409	£56,411

		interval)	interval)				

Neutropenia	-0.08973	-0.088, (Lower confidence interval)	-0.091 (Upper confidence interval)		£56,410	£56,413	£56,406
Resultant PFS Values (applied to both arms)	PFS vem = 0.806 PFS dac = 0.767	Dac PFS utility (0.767) applied to both treatments	Vem PFS utility (0.806) applied to both treatments		£56,410	£58,847	£57,488
Costs							
Pharmacy costs when vemurafenib dispensed	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£56,410	£56,317	£56,503

Dacarbazine Pharmacy Cost	£13	£6.63 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£19.37 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£56,410	£56,468	£56,351
Dacarbazine Administration Cost	£248	£126.48 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£369.52 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£56,410	£57,528	£55,292
		£192.78	£563.22				

Monthly PFS BSC Cost	£378	(Lower confidence interval if standard error = 1/4 base case value (assumption))	(Upper confidence interval if standard error = 1/4 base case value (assumption))		£56,410	£55,133	£57,687
Monthly PD BSC Cost	£378	£192.78 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£563.22 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£56,410	£54,455	£58,364
Terminal Care Cost	£5,401	£2,754.51 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£8,047.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£56,410	£56,522	£56,298

Cost of Rash	£126.96	£64.75 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£189.17 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£56,410	£56,401	£56,419
Cost of Neutropenia	£407.38	£207.76 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£607.00 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£56,410	£56,439	£56,380
Cost of cuSCC/ keratocanthoma	£115	£58.65	£171.35	£56,410	£56,396	£56,424

		(Lower confidence interval if standard error = 1/4 base case value (assumption))	(Upper confidence interval if standard error = 1/4 base case value (assumption))				

Patient Characteristics						
Age	54	45	65	£56,410	£55,732	£60,476
BRAF mutation incidence	48%	40%	60%	£56,410	£56,548	£56,272
General Parameters						
Time Horizon	30 years	20 years	-	£56,410	£61,475	-
Costs Discount Rate	3.5%	0%	6%	£56,410	£59,960	£54,679
Health Outcomes Discount Rate	3.5%	0%	6%	£56,410	£42,054	£66,175
Both Discount Rates	3.5%	0%	6%	£56,410	£44,679	£64,150

Figure 1: Tornado Diagram (with [redacted]% discount)

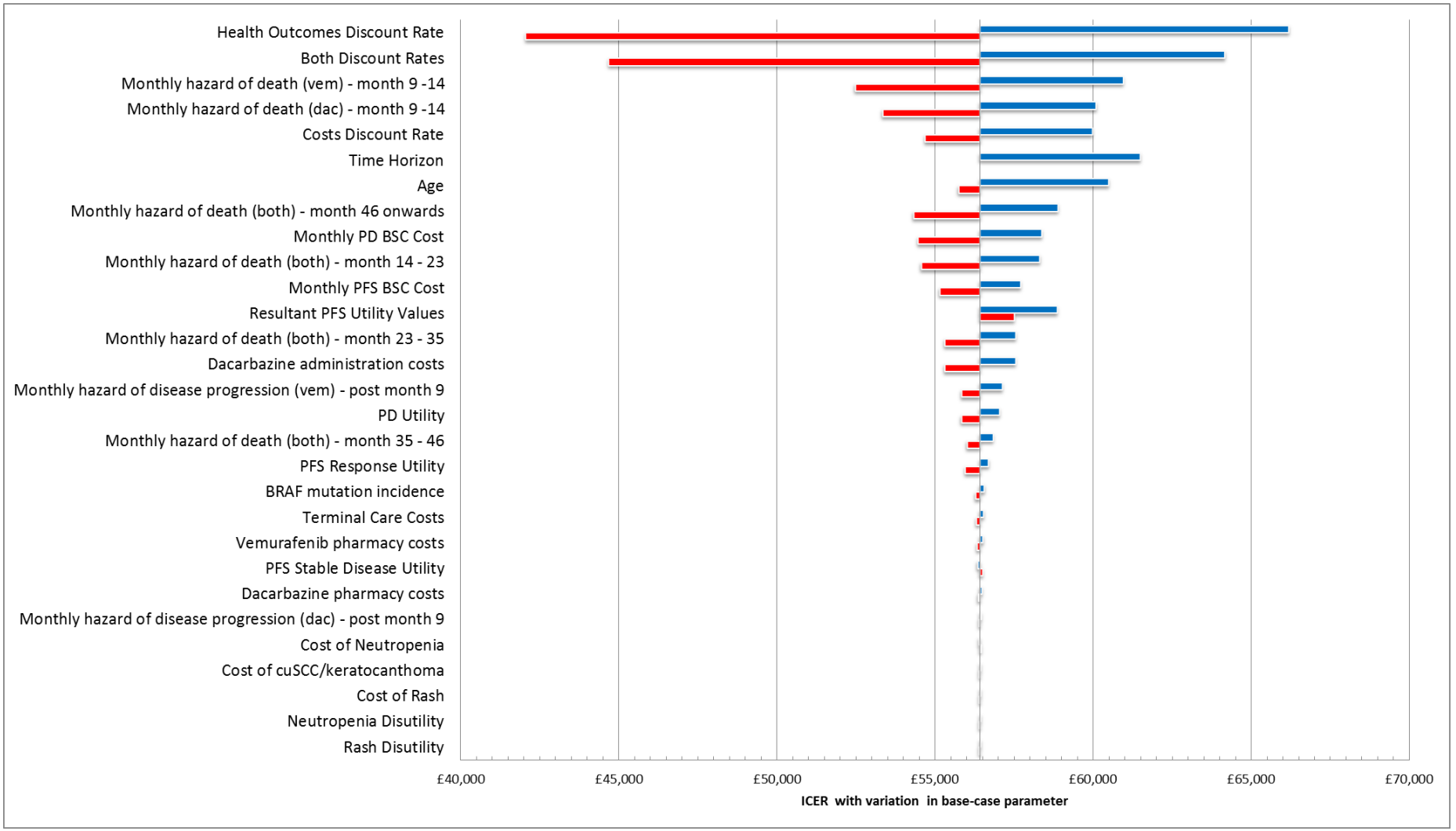


Table 6: OS Sensitivity Analyses Results

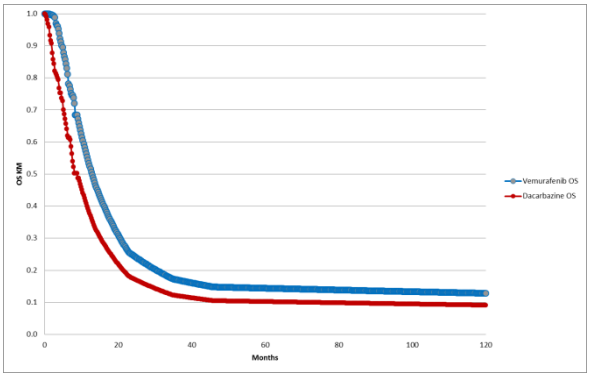
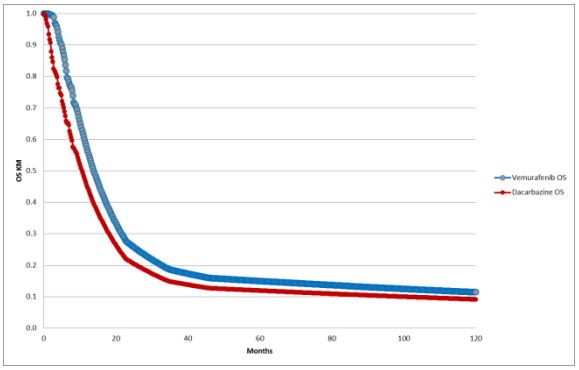
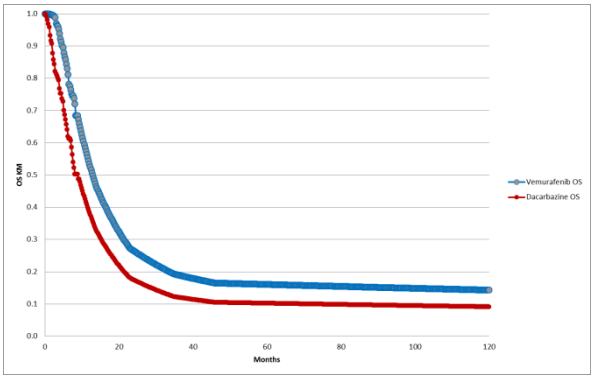
Scenario	Description	OS Curve	ICER
1	Base-Case		£56,410
2	October Cut		£75,489
3	Base-Case with 34 month treatment effect		£46,856

Table 7: Utility Sensitivity Analyses Conducted

Scenario	Description	ICER
1	Base-Case	£56,410
2	Base-Case with higher Hodi mapped PD utility value used to reflect the potential for patients in 'tail' of survival curve to have lower tumour burden and therefore improved HRQoL	£49,079
3	Hodi EORTC-QLQ-C30 mapped values	£50,052
4	Hodi SF-36 mapped values	£61,842

Budget Impact of NICE approval of vemurafenib

Table 8: Budget Impact of NICE approval (with [redacted]% discount)

Year	2012	2013	2014	2015	2016
Eligible Population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 9: Base-case PSA results – with [redacted] % discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Dacarbazine	[redacted]	[redacted]	[redacted]					
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,766	£56,766

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

Figure 2: PSA Scatter-plot (3,000 simulations)

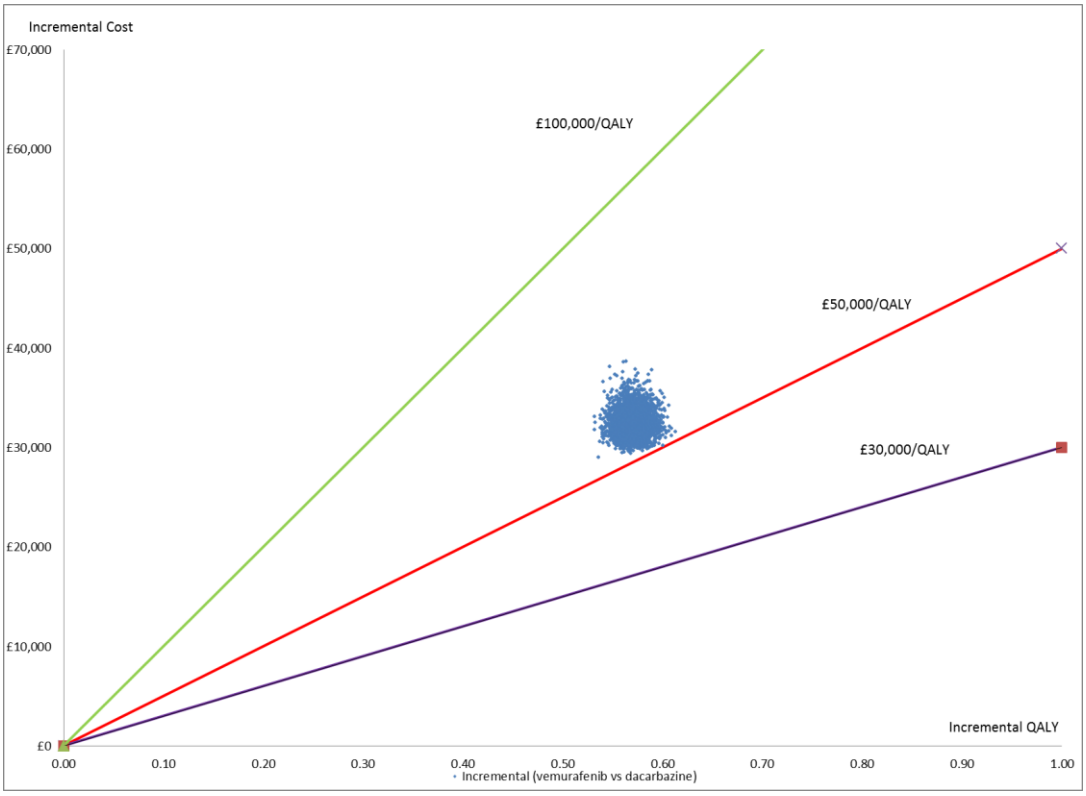
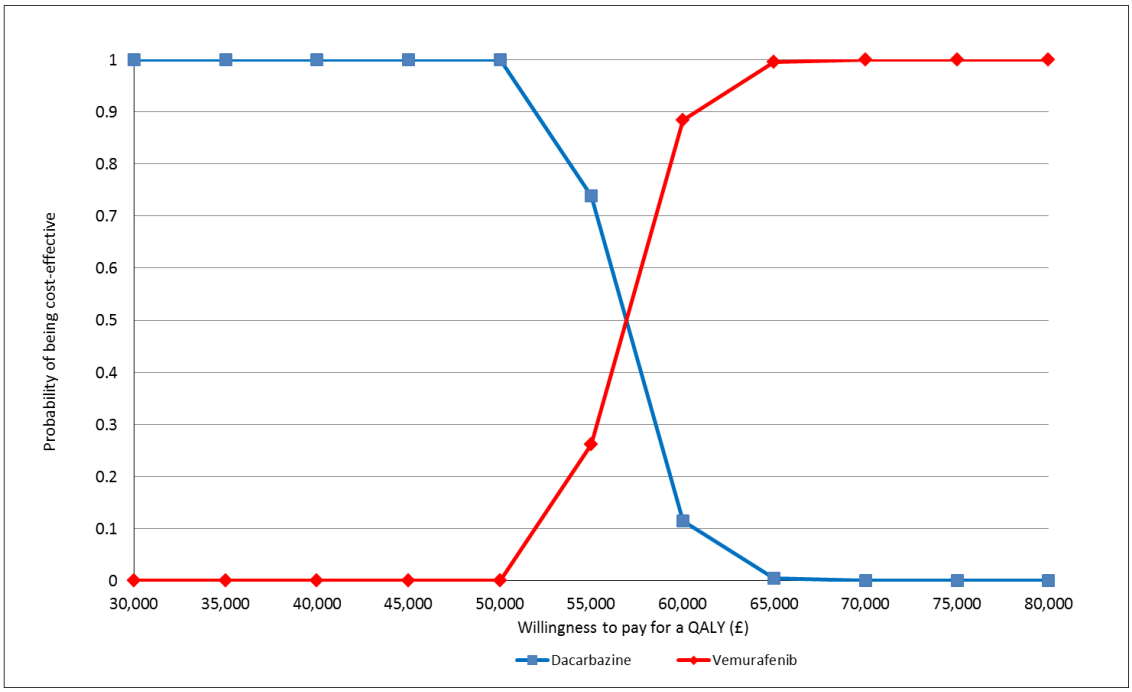


Figure 3: Cost Effectiveness Acceptability Curves



At a threshold of £50,000/QALY vemurafenib would be considered cost-effective in 0% of simulations conducted.

At a threshold of £55,000/QALY vemurafenib would be considered cost-effective in 26.13% of simulations conducted.

At a threshold of £60,000/QALY vemurafenib would be considered cost-effective in 88.40% of simulations conducted.

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.

5 References

Claxton, K., Paulden, M., Gravelle, H., Brouwer, W., & Culyer, A. J. 2011, "Discounting and decision making in the economic evaluation of healthcare technologies", *Health economics*, vol. 20, no. 1, pp. 2-15.