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.

The proposed patient access scheme is about providing access to pazopanib, which is indicated for the first-line treatment of advanced renal cell carcinoma and for patients who have received prior cytokine therapy for advanced disease.

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

Background information

Until recently, the cytokines, interferon-α (IFN) and interleukin-2 (IL-2), were the only available treatments for patients with advanced renal cell carcinoma (RCC). However, their use has been limited by their modest response rates and significant toxicity. The introduction of agents targeted at the VEGF and related pathways has greatly improved the management of this malignancy, with significant clinical activity demonstrated in both treatment-naïve and cytokine pre-treated patients. However, only sunitinib has been recommended by NICE for the first-line treatment of RCC.

Despite improvements in efficacy, the toxicities observed with sunitinib and other VEGF targeted therapies remain a challenge. Consequently there is an unmet need for alternative treatments that offer a favourable side effect profile without compromising efficacy for patients with RCC.

Pazopanib offers a clinically effective oral option with a different, manageable tolerability profile compared with other tyrosine kinase inhibitors (TKI), for the first-line treatment of patients with advanced RCC. In the pivotal phase III RCT, first-line treatment with pazopanib significantly increased progression free survival (PFS) compared with placebo / best supportive care (11.1 vs. 2.8 months; $p<0.001$). The majority of adverse events were mild to moderate and there was a low incidence of grade 3/4 fatigue, stomatitis/mucositis, and hand-foot syndrome.

Even though there are currently no head-to-head comparative data, qualitative and formal indirect comparison of data from the pivotal clinical trials suggests that pazopanib has a favourable safety profile compared with sunitinib with similar efficacy in patients with advanced RCC, giving clinicians and patients choice.

The CHMP adopted a positive opinion for pazopanib in advanced RCC on 19th February 2010 due to pazopanib having “clear clinical benefits, with a distinct pharmacodynamic profile, considered to offer major advantage in the

context of the therapies for this disease" [Votrient EPAR, 14 June 2010]. Conditional Marketing Authorisation was granted on 14th June 2010. This is a conditional licence based upon the outcome of an ongoing head-to-head study (the COMPARZ study) of pazopanib vs. sunitinib in advanced RCC.

The COMPARZ study was set up to address the uncertainty surrounding the clinical effectiveness of pazopanib compared with the current standard of care, sunitinib.

COMPARZ is a non-inferiority Phase III randomised controlled clinical study to evaluate the efficacy and safety of pazopanib versus the TKI, sunitinib. As a condition of the licence, GSK has agreed with EMA to submit results from this study in order to provide robust clinical data to compare the efficacy and safety of pazopanib versus sunitinib. The analysis will be appropriately powered to demonstrate non-inferiority with a margin of 1.22 with respect to progression-free survival. Clear timelines for expected evidence and deliverables have been agreed with the EMA.

The commitment to the EMA is a non-inferiority analysis of pazopanib compared to sunitinib using data integrated from two clinical trials. The integrated analysis will be performed when 794 PFS events have been observed. The non-inferiority margin is 1.22. That means that the upper bound of the confidence interval must be at or below 1.22 in order to declare non-inferiority. Using the protocol-dictated sample size and margin, it is possible to back-calculate that the required point estimate of the hazard ratio will be 1.06 or less in order to declare non-inferiority[1].

Within the UK, recruitment for COMPARZ is now complete and 125 UK patients have been randomised. Globally, 926 patients have been randomised.

As part of the STA process NICE is evaluating pazopanib as first line treatment of advanced RCC and the final scope for this appraisal requires pazopanib to be compared with sunitinib. The initial submission for the appraisal was 16th April 2010 based on the pivotal RCT for which GSK received mature overall survival data in June 2010.

Pfizer is making sunitinib available to the NHS under a patient access scheme (PAS) which offers the first treatment cycle free. NICE considered that sunitinib fulfilled the criteria for a life-extending, end-of-life treatment and, in March 2009, recommended it as a first-line treatment option for people with advanced RCC, with this PAS.

The rationale behind the proposed scheme for pazopanib is two-fold:

PART A - achieving equivalence to the cost of sunitinib to the NHS

[1] Note these calculations are based on an unadjusted HR, even though the final analysis will be stratified because this is a best estimate given it is not possible to entirely predict how the stratification will impact the results.

From the time of publishing of positive NICE guidance for pazopanib in first line advanced RCC, GSK will provide pazopanib to the NHS at a cost which is equivalent to the effective cost of sunitinib to the NHS (including the sunitinib PAS), but without additional administrative burden. This will be achieved through list price parity and a straight discount at the point of invoice.

AND

[redacted]

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

The patient access scheme is a straight discount (to be implemented from positive NICE guidance, expected February 2010), together with an expected value rebate and subsequent price reduction, in the event that pazopanib fails to meet the conditional licence requirements by June 2012, as stipulated by EMA.

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 proposed straight discount [redacted] would apply to all patients who have the condition(s) for which pazopanib is licensed, including any new indications that might be licensed during the lifetime of the scheme. The scheme would remain in place until NICE reviews pazopanib for advanced renal cell carcinoma.

If pazopanib secures a new licensed indication prior to NICE review, an alternative scheme may be required for the new indication. In the event that an alternative scheme was deemed necessary by GSK, GSK would seek to develop such a scheme in consultation with PASLU to enable patients to benefit from access to the pazopanib without undue burden to NHS.

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.**

PART A - The straight discount will apply at the point of invoicing from the time of positive NICE guidance. No additional criteria will need to be met.

[redacted]

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

As stated above the scheme criteria are based on COMPARZ study demonstrating non-inferiority versus sunitinib within a margin of 1.22 in respect of progression-free survival as indicated by EMA conditional licence. Hence, it can be inferred that 100% of the population treated with pazopanib in England and Wales will be covered by the proposed scheme.

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

PART A - For every pack of pazopanib ordered, a straight discount will be given automatically by GSK at the point of invoice. Details of this discount are provided in section 4.3. No additional paperwork or forms will be required. This is further discussed in section 5.2.2

[redacted]

[redacted]

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.

No additional information will need to be collected. The list price of pazopanib, which has been submitted to the Department of Health, has been calculated to be the same list price per day as sunitinib. Pazopanib will be available in 2 pack sizes as follows:

- 200mg tablets, 30 per pack at a cost of £560.50 per pack

- 400mg tablets, 30 per pack at a cost of £1121.00 per pack

For every pack of pazopanib ordered, a straight discount will be given automatically by GSK at the point of invoice as part of the scheme, in order to provide pazopanib at the same effective cost to the NHS as sunitinib (including the sunitinib PAS) as at the date of submission of the pazopanib scheme.

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

A flow diagram for part A and B of the scheme is provided in appendix 1

3.10 **Please provide details of the duration of the scheme**.

Subject to a positive NICE guidance, the proposed scheme would be in place until NICE review, subject to the normal NICE review process, and subject to Department of Health agreement. As stated earlier the outcome of the COMPARZ study will be available in Q2 2012, and it is expected that these results will trigger a new review of this STA. If GSK secures a new licensed indication for pazopanib prior to NICE review, the straight discount (PART A) will apply to patients within the new indication. No additional monitoring or data collection will be required for the duration of the scheme.

[redacted]

[redacted]

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?

PASLU review did not identify any equity or equality issues relating to the scheme, that is, issues that may cause unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief.

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.**

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.**

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.

Not applicable

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 economic model incorporates a 12.5% straight discount from the pazopanib list price (Part A). Thus the daily acquisition cost of pazopanib was changed from £74.73 to £65.39. The incorporation of part B into the economic model is discussed in section 5.2.5.

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.

Clinical effectiveness estimates utilised in the model are displayed in table 4.1.

Table 4.1. Effectiveness estimates used in the economic model

		PFS			OS			sources
		Est.	95%CI		Est.	95%CI		
IFN	λ	0.154			0.070			**PFS:** Motzer 2007 ASCO
Weibull distribution	γ	0.895			0.830			**OS:** TA169/ Figlin 2008
HR vs. BSC	Pazopanib	0.360	0.240	0.550	0.501	0.140	2.350	**PFS:** VEGF105192 IRC Scan dates
								OS: VEGF105192 RPSFT weighted unadjusted model
	IFN	0.704	0.580	0.854	0.799	0.674	0.948	**Pooled analysis**
								PFS: Negrier (2007), Hancock/MRC (2000) and Pyrhonen (1999)
								OS: Negrier (2007) , Hancock/MRC (2000), Pyrhonen (1999), Kriegmair (1995), Steineck (1990)
HR vs. IFN	Pazopanib	0.512	0.326	0.802	0.627	0.173	2.269	**Indirect comparison**
								HR Paz vs. BSC ÷ HR IFN vs BSC
	Sunitinib	0.539	0.431	0.643	0.647	0.483	0.870	**PFS**: Motzer JCO 2009 (Final analysis)
								OS: Motzer JCO 2009 (Final analysis-Pts w/PS tx excl.)

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'.

In their draft positive advice to DH, PASLU states that "The patient access scheme liaison unit (PASLU) review identified no additional administrative burden to the NHS for part A of the scheme. [redacted]

[redacted]

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.

Not applicable

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[2]

- **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).

Cost effectiveness results with and without a 12.5% discount from the pazopanib list price are displayed in table 4.2 and table 4.3 respectively.

Table 4.2. Base case cost-effectiveness results

				vs. BSC			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987				
IFN	8,379	2.020	1.249	4,294	0.421	0.262	16,395

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

Sunitinib	36,179	3.018	1.898	32,094	1.420	0.911	35,231
Pazopanib	40,441	3.097	1.966	36,356	1.499	0.979	37,126

				vs. IFN			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987	-4,294	-0.421	-0.262	16,395
IFN	8,379	2.020	1.249				
Sunitinib	36,179	3.018	1.898	27,799	0.999	0.649	42,832
Pazopanib	40,441	3.097	1.966	32,062	1.077	0.717	44,697

				vs. Sunitinib			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987	-32,094	-1.420	-0.911	35,231
IFN	8,379	2.020	1.249	-27,799	-0.999	-0.649	42,832
Sunitinib	36,179	3.018	1.898				
Pazopanib	40,441	3.097	1.966	4,263	0.079	0.068	62,414

Table 4.3. Base case cost-effectiveness results incorporating a 12.5% discount

				vs. BSC			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987				
IFN	8,379	2.020	1.249	4,294	0.421	0.262	16,395
Sunitinib	36,179	3.018	1.898	32,094	1.420	0.911	35,231
Pazopanib	36,301	3.097	1.966	32,216	1.499	0.979	32,898

				vs. IFN			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987	-4,294	-0.421	-0.262	16,395
IFN	8,379	2.020	1.249				
Sunitinib	36,179	3.018	1.898	27,799	0.999	0.649	42,832
Pazopanib	36,301	3.097	1.966	27,921	1.077	0.717	38,925

				vs. Sunitinib			
Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£)**
BSC	4,085	1.598	0.987	-32,094	-1.420	-0.911	35,231
IFN	8,379	2.020	1.249	-27,799	-0.999	-0.649	42,832
Sunitinib	36,179	3.018	1.898				
Pazopanib	36,301	3.097	1.966	122	0.079	0.068	1,790

4.8 Please present in separate tables the incremental results as follows. [3]

- **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.

Incremental cost-effectiveness results with and without a 12.5% discount from the pazopanib list price are displayed in tables 4.4 and 4.5 respectively.

Table 4.4. Incremental base case results

Technology	Total Cost £	Total QALY	Incremental cost £	Incremental QALY	ICERs vs. baseline £/QALY	Incremental analysis £/QALY
BSC (baseline)	4,085	0.987				
IFN	8,379	1.249	4,294	0.262	16,395	16,395
Sunitinib	36,179	1.898	27,799	0.649	35,231	extendedly dominated by pazopanib
Pazopanib	36,301	1.966	122	0.068	32,898	38,925
QALY, quality adjusted life year; ICERs, incremental cost-effectiveness ratios						

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

Figure 4.1. Incremental cost effectiveness

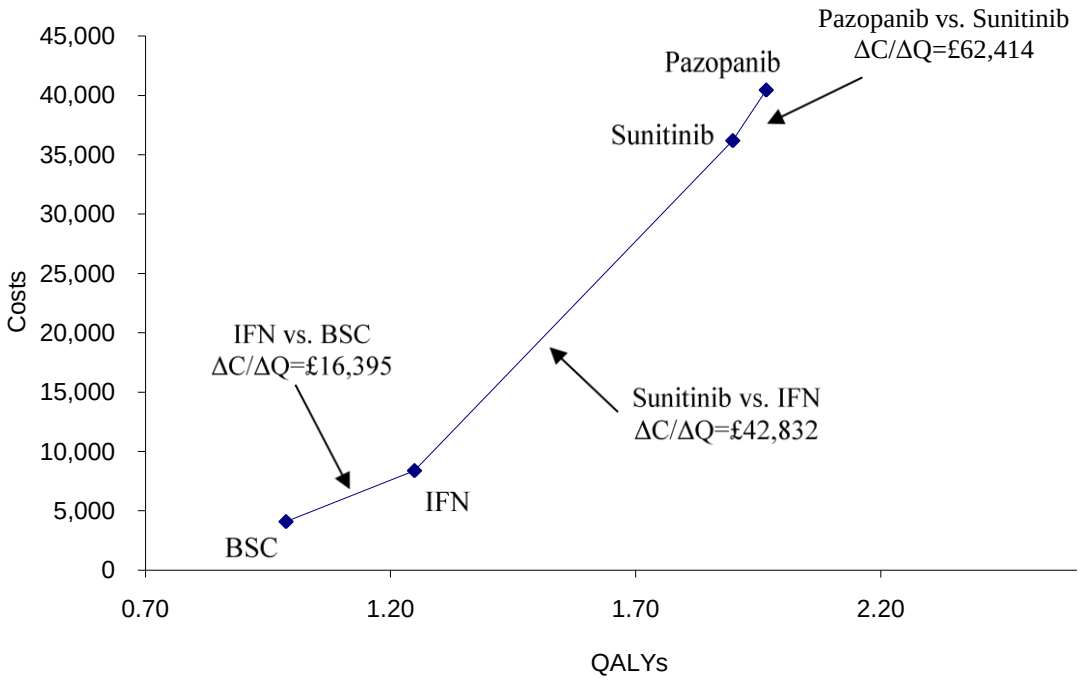
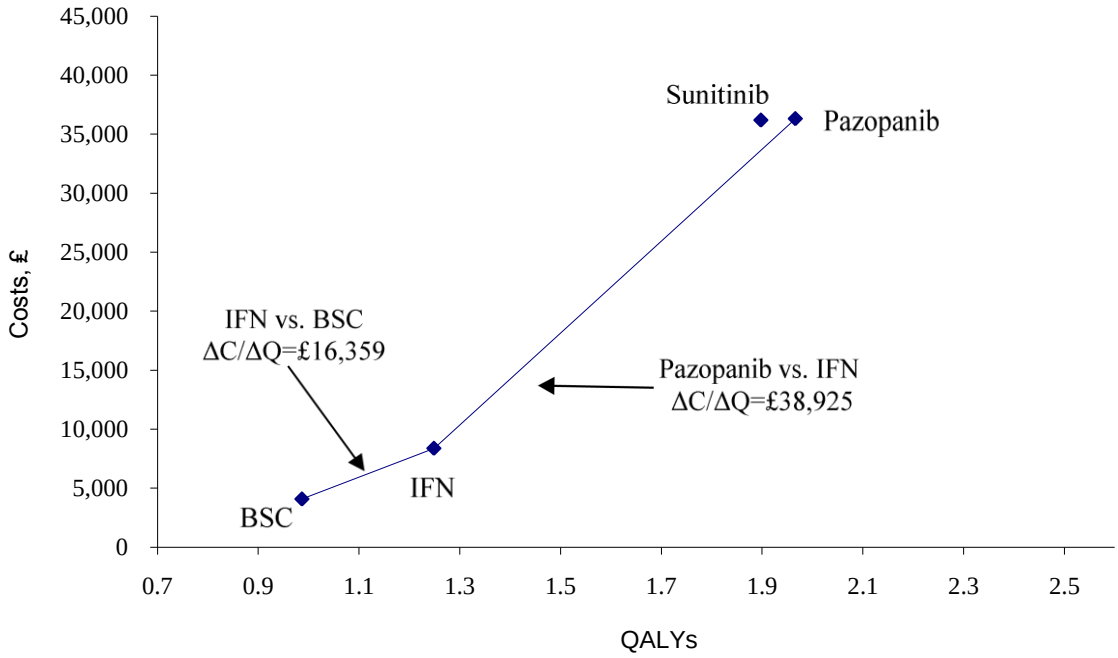


Table 4.5. Incremental base case results incorporating a 12.5% discount

Technology	Total Cost £	Total QALY	Incremental cost £	Incremental QALY	ICERs vs. baseline £/QALY	Incremental analysis £/QALY
BSC (baseline)	4,085	0.987				
IFN	8,379	1.249	4,294	0.262	16,395	16,395
Sunitinib	36,179	1.898	27,799	0.649	35,231	extendedly dominated by pazopanib
Pazopanib	36,301	1.966	122	0.068	32,898	38,925
QALY, quality adjusted life year; ICERs, incremental cost-effectiveness ratios						

Figure 4.2. Incremental cost-effectiveness analysis incorporating a 12.5% discount



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 analyses as per the original submission are presented in table 4.6. These incorporate a 12.5% discount from the pazopanib list price. In addition to this, table 4.7 shows cost-effectiveness estimates employing different methods to account for cross over in VEG105192 for OS estimates for pazopanib versus BSC.

Table 4.6. Deterministic sensitivity analysis for base case

	Pazopanib		Difference Pazopanib vs.								
			Sunitinib			IFN			BSC		
	Costs, £	QALYs	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £	Costs, £	QALYs	ΔC/ΔQ, £
Base Case	36,301	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
HR PFS pazopanib vs. IFN=0.326	58,196	2.089	22,017	0.192	114,927	49,816	0.841	59,263	54,111	1.103	49,079
HR PFS pazopanib vs. IFN =0.802	23,300	1.893	-12,878	-0.005	2,625,026	14,921	0.644	23,165	19,215	0.906	21,208
HROS pazopanib vs. IFN=0.106	40,826	2.942	4,647	1.044	4,451	32,447	1.693	19,164	36,741	1.955	18,793
HROS pazopanib vs. IFN =1.750	32,264	1.101	-3,915	-0.797	4,911 †	23,885	-0.148	Dominated	28,179	0.114	247,380
Cost IFN admin=0.5 x base-case	36,301	1.966	122	0.068	1,790	28,187	0.717	39,295	32,216	0.979	32,898
Cost IFN admin=1.5 x base-case	36,301	1.966	122	0.068	1,790	27,656	0.717	38,554	32,216	0.979	32,898
Cost therapy initiation=0.5 x base-case	36,230	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
Cost therapy initiation=1.5 x base-case	36,372	1.966	122	0.068	1,790	27,921	0.717	38,925	32,216	0.979	32,898
Other Cost PFS=0.5 x base-case	35,065	1.966	58	0.068	847	27,290	0.717	38,045	31,393	0.979	32,058
Other Cost PFS=1.5 x base-case	37,536	1.966	187	0.068	2,733	28,552	0.717	39,804	33,039	0.979	33,739
Other Cost PPS=0.5 x base-case	33,996	1.966	115	0.068	1,687	27,434	0.717	38,245	31,453	0.979	32,119
Other Cost PPS=1.5 x base-case	38,606	1.966	129	0.068	1,893	28,409	0.717	39,604	32,979	0.979	33,677
Cost of AEs=0.5 x base-case	36,255	1.966	198	0.068	2,899	27,930	0.717	38,936	32,188	0.979	32,870
Cost of AEs=1.5 x base-case	36,346	1.966	46	0.068	681	27,913	0.717	38,913	32,244	0.979	32,927
Incidence of AEs=lower 95% confidence interval	36,231	1.975	153	0.071	2,145	27,884	0.724	38,536	32,162	0.986	32,622
Incidence of AEs=upper 95% confidence interval	36,518	1.949	192	0.058	3,309	28,095	0.703	39,982	32,403	0.965	33,595

Utility PFS=0.75 x base-case	36,301	1.424	122	0.055	2,242	27,921	0.529	52,803	32,216	0.717	44,932
Utility PFS=1.75 x base-case	36,301	2.508	122	0.082	1,489	27,921	0.906	30,823	32,216	1.242	25,949
Utility PFS=0.65	36,301	1.811	122	0.064	1,899	27,921	0.663	42,085	32,216	0.904	35,624
Utility PFS=0.75	36,301	2.121	122	0.072	1,692	27,921	0.771	36,206	32,216	1.054	30,560
Utility PFS and PPS that of healthy person (0.78), no decrement for Aes	36,301	1.983	122	0.055	2,240	27,921	0.715	39,052	32,216	0.988	32,617
Decrement utility w/Progression 0.5 x base-case	36,301	2.059	122	0.069	1,782	27,921	0.737	37,890	32,216	1.010	31,899
Decrement utility w/Progression 1.5 x base-case	36,301	1.874	122	0.068	1,797	27,921	0.698	40,018	32,216	0.949	33,962
Decrement in utility with AEs=0.5 x base-case	36,301	1.974	122	0.061	1,990	27,921	0.716	38,988	32,216	0.983	32,757
Decrement in utility with AEs=1.5 x base-case	36,301	1.958	122	0.075	1,626	27,921	0.718	38,861	32,216	0.975	33,041
Duration of utility with Aes=0.5 x base-case	36,255	1.966	198	0.068	2,899	27,930	0.717	38,936	32,188	0.979	32,870
Duration of utility with Aes=1.5 x base-case	36,346	1.966	46	0.068	681	27,913	0.717	38,913	32,244	0.979	32,927
Decrement in utility with AEs from Oxford Outcomes	36,312	1.940	84	0.067	1,240	27,908	0.699	39,932	32,165	0.982	32,756
HR for PFS and OS for pazopanib vs. IFN calculated using only the MRC study (PFS HR=0.545, OS HR=0.460)	34,038	1.844	-2,141	-0.054	39,382	25,659	0.595	43,148	29,953	0.857	34,967
HR for PFS and OS for pazopanib vs. IFN calculated excluding the VBL studies (PFS HR=0.495, OS HR=0.400)	37,076	2.133	897	0.235	3,811	28,697	0.884	32,444	32,991	1.146	28,778
HR for PFS for pazopanib vs. IFN adjusted to reflect % w/ECOG=0/1 in sunitinib pivotal trial (HR=0.455)	39,519	1.984	3,341	0.086	38,658	31,140	0.735	42,342	35,434	0.997	35,528

HRs for OS for pazopanib vs. IFN using HR for pazopanib vs. placebo in VEG105192 without censoring on cross-over or adjustment for baseline covariates (HR=0.930)	33,767	1.420	-2,411	-0.478	5,044	25,388	0.171	148,462	29,682	0.433	68,560
HR for OS for sunitinib vs. IFN based on final analysis (HR=0.820)	36,301	1.966	1,679	0.404	4,156	27,921	0.717	38,925	32,216	0.979	32,898
HRs for PFS and OS for pazopanib vs. IFN = HRs for sunitinib vs. IFN (PFS HR=0.539, OS HR=0.647)	34,647	1.912	-1,532	0.014	dominant	26,267	0.663	39,634	30,562	0.925	33,051
HR for OS for pazopanib vs. IFN = HR for sunitinib vs. IFN (HR=0.647)	36,085	1.920	-93	0.022	dominant	27,706	0.671	41,300	32,000	0.933	34,306
HR for OS for pazopanib vs. IFN to make PPS equal to that of sunitinib (HR=0.629)	36,279	1.961	100	0.064	1,578	27,899	0.713	39,152	32,194	0.975	33,035
Time Frame=5 years	33,283	1.573	-51	0.046	dominant	25,549	0.464	55,067	29,529	0.658	44,907
Time Frame=15 years	36,942	2.089	183	0.079	2,333	28,450	0.815	34,897	32,818	1.093	30,020
Annual discount rate=0%	38,816	2.181	105	0.078	1,346	29,950	0.831	36,043	34,442	1.129	30,518
Annual discount rate=6%	35,345	1.887	132	0.065	2,035	27,150	0.676	40,156	31,370	0.925	33,917

† Pazopanib is less costly and less effective than comparator; value represents CE of comparator vs Pazopanib

Table 4.7. Summary of cost-effectiveness estimates for all final OS analyses incorporating a 12.5% discount from list price for pazopanib

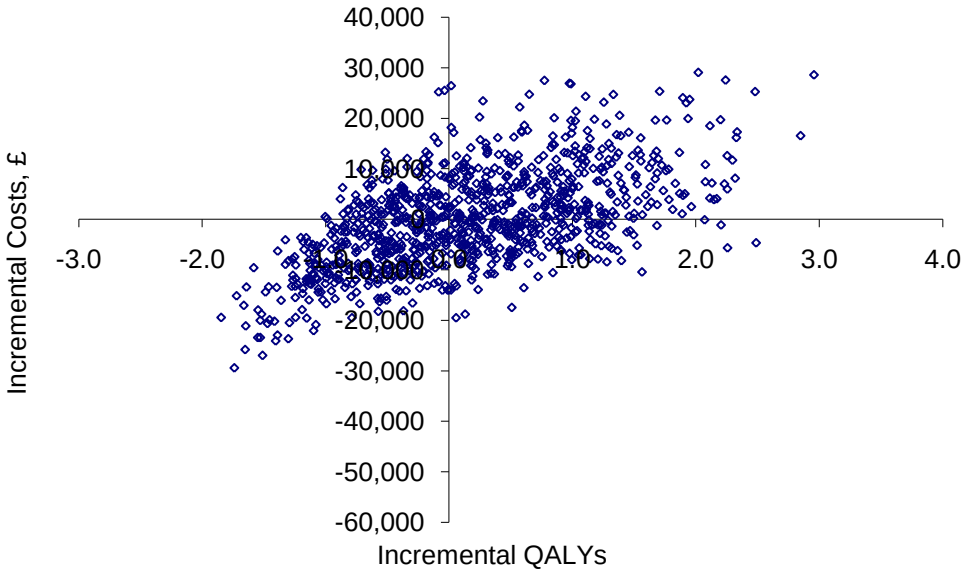
Final OS analysis	HR vs. IFN	Pazopanib			ICER vs.		
		Costs	LYs	QALYs	Sunitinib	IFN	BSC
ITT	1.264	£32,099	1.581	1.071	£4,936†	Dominated	£322,237
Cox Model censored on cross over	0.801	£34,676	2.503	1.616	£5,327†	£71,648	£48,638
IPCW	0.803	£34,661	2.497	1.613	£5,139†	£72,274	£48,877
RPSFT weighted unadjusted	0.627	£36,301	3.097	1.966	£1,790	£38,925	£32,898
RPSFT unweighted adjusted	0.388	£39,689	4.335	2.697	£4,394	£21,625	£20,824
No post-study therapy	0.476	£38,241	3.806	2.385	£4,238	£26,293	£24,438
†Comparator is more costly and more effective than pazopanib. Ratio is cost-effectiveness of comparator vs. pazopanib							

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

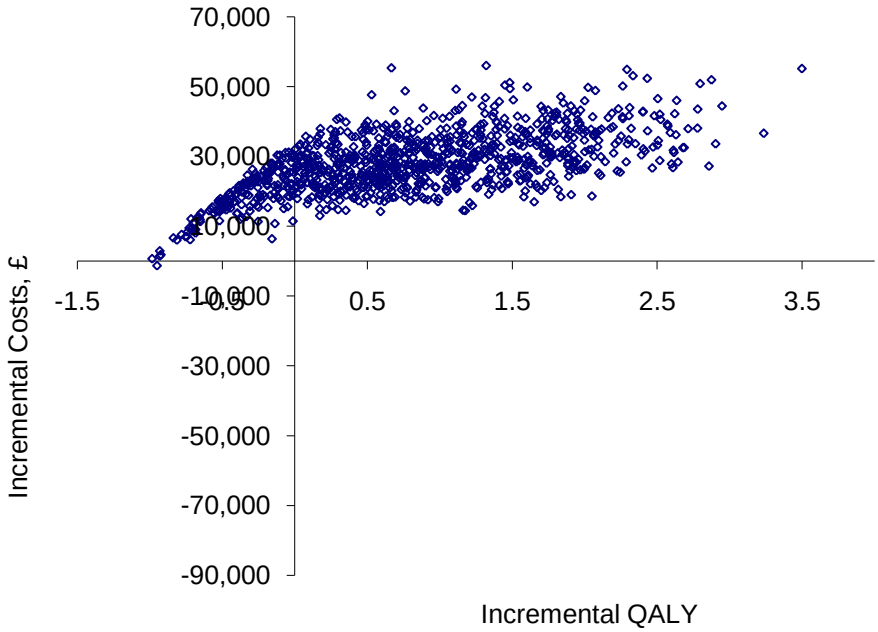
Probabilistic sensitivity analysis for the base case is shown in figure 4.3. A cost-effectiveness acceptability curve is presented in figure 4.3.

Figure 4.3. Scatterplot of PSA (1,000 runs) – Weighted RPSFT (+12.5% discount). A vs. sunitinib; B vs. IFN; C vs. BSC

A. Pazopanib vs. sunitinib



B. Pazopanib vs. IFN



C. Pazopanib vs. BSC

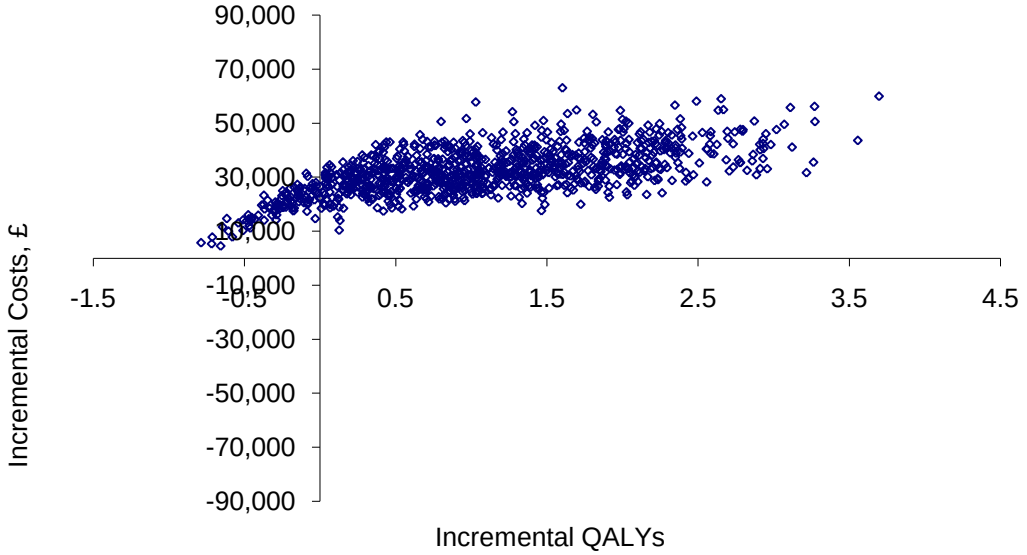
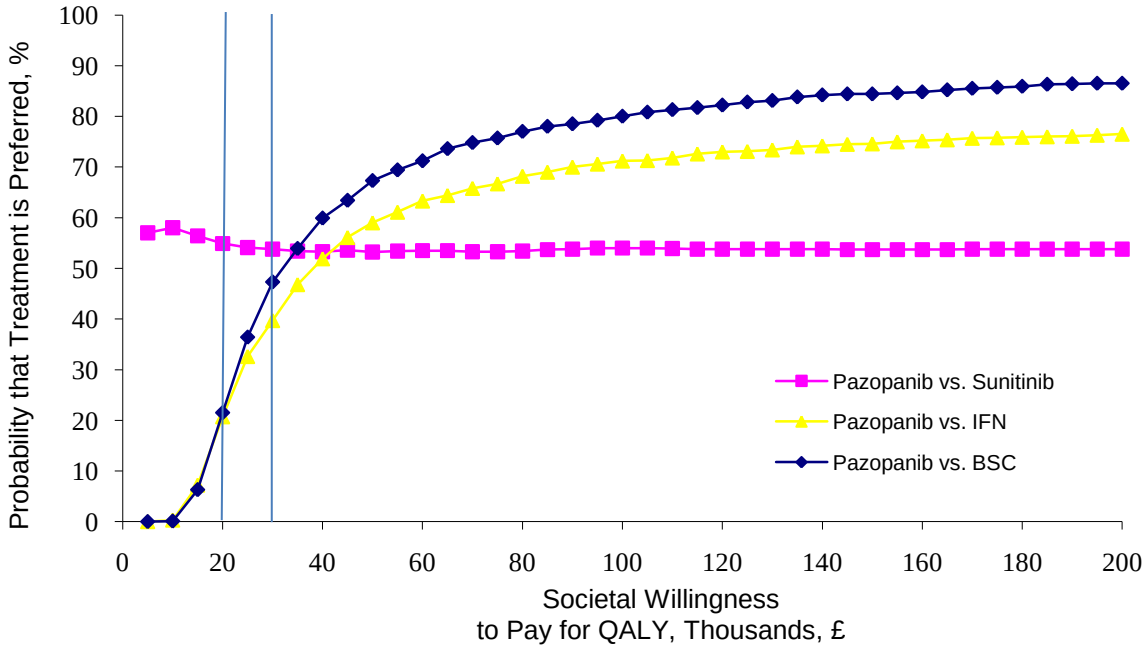


Figure 4.4. Cost-effectiveness acceptability curve – weighted RPSFT (+12.5% discount): pair-wise comparisons of pazopanib vs. sunitinib, pazopanib vs. IFN, and pazopanib vs. BSC



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

Scenario analysis was not presented as part of the main submission. Extensive deterministic sensitivity analysis is presented in table 4.6.

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.

Not applicable.

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.

Table 4.8 presents ICERs with and without the 12.5% discount from the pazopanib list price.

Table 4.8. Results showing the impact of patient access scheme on ICERs

	ICER for pazopanib versus:					
	Sunitinib		IFN		BSC	
	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS
Base case	£62,414	£1,790	£44,697	£38,925	£37,126	£32,898

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.

Not applicable

Appendix B: Details of outcome-based schemes

5.1.2 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.

5.1.3 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.**

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5.1.4 **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.**

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).**

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5.1.5 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

5.1.6 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.

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5.1.7 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.

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5.1.8 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.

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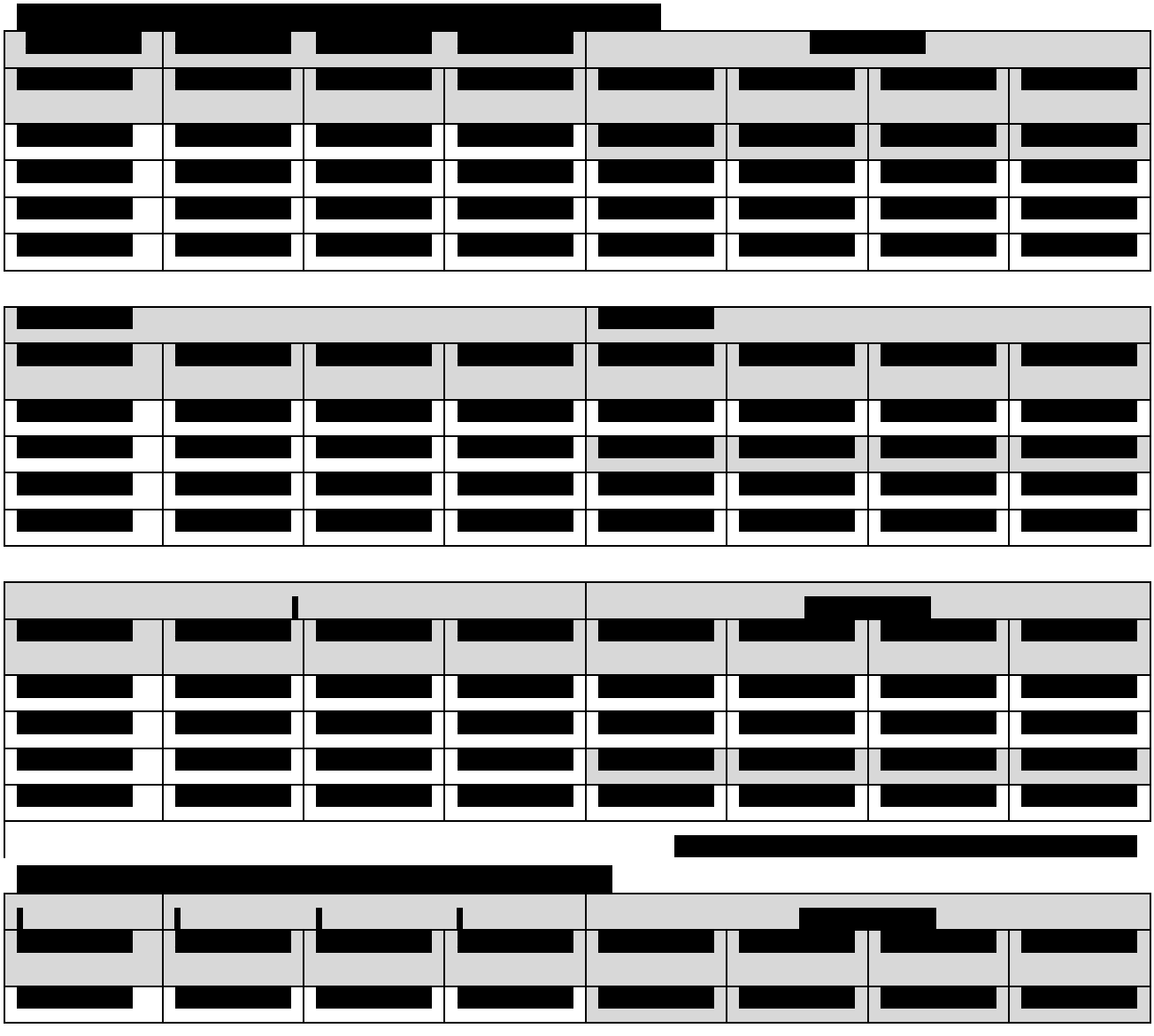

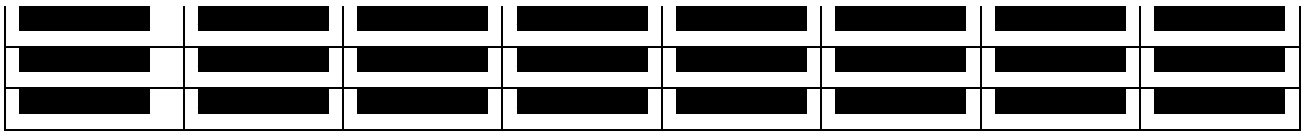

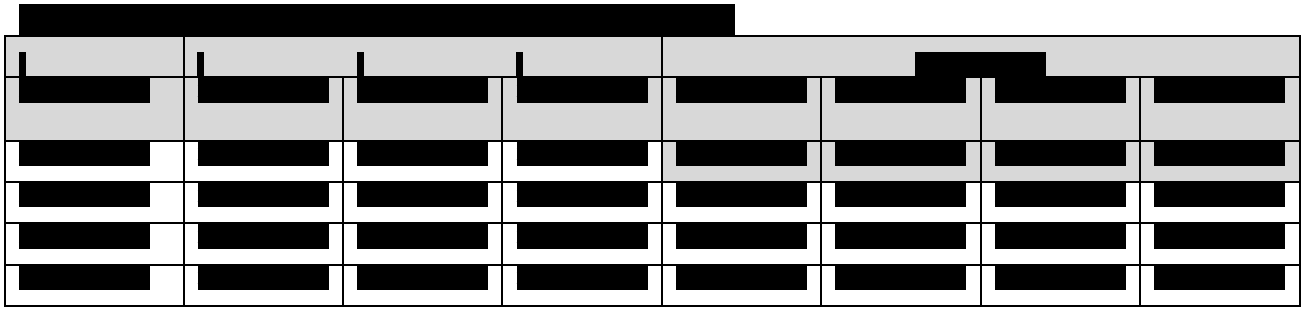

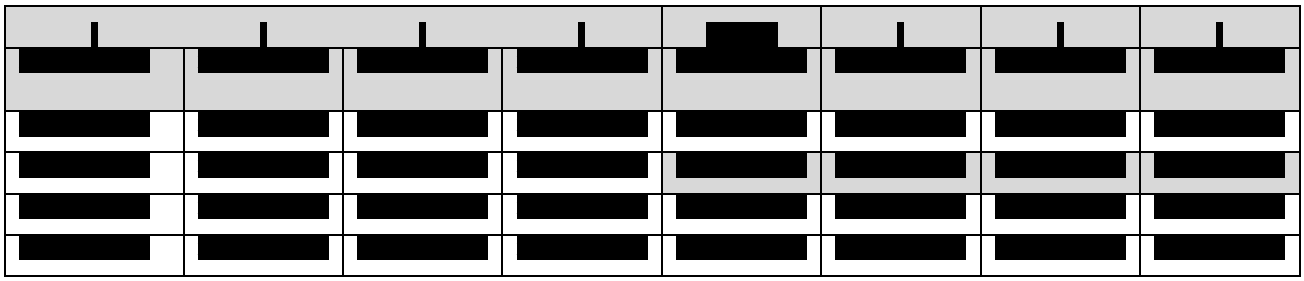

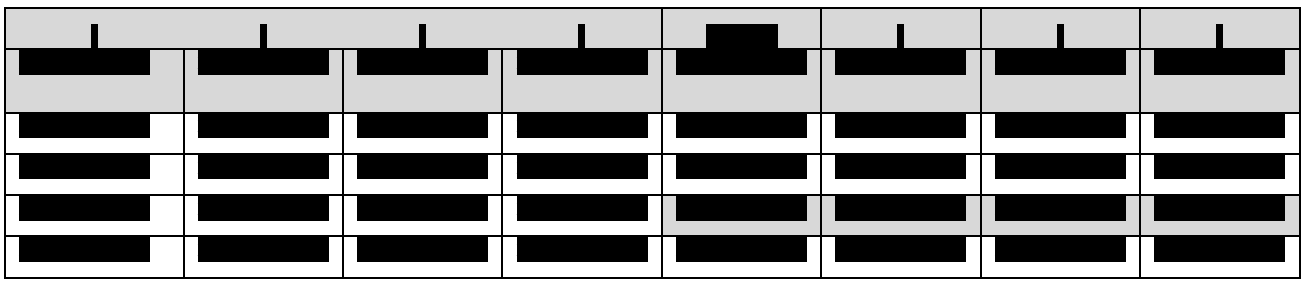

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5.1.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

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.

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APPENDIX 1. Pazopanib patient access scheme flow diagram