NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology Appraisals

Patient Access Scheme Submission Template –

Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer

CONTENT

Please note that the Patient Access Scheme described in this template has not yet been approved by DH for evaluation by NICE. However, in order to provide NICE and the ERG with early sight of the scheme we are tabling it now with our main submission 'for information'.

We understand that a decision from DH regarding whether the scheme can be evaluated by NICE will follow imminently.

Details of the patient access scheme

1.1. Please provide the title of the appraisal for which the patient access scheme applies.

Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer.

1.2. Please provide any relevant background details and the rationale for developing the patient access scheme.

Bevacizumab (brand name: Avastin) is the first in an innovative class of drugs that act as anti-angiogenic agents. Angiogenesis inhibitors are drugs which are designed to stop tumours from developing a blood supply, a pre-requisite for tumour growth and metastasis (tumour spreading). Bevacizumab works by inhibiting the action of VEGF, a specific angiogenesis growth factor that binds to receptors on blood vessels and stimulates the formation of new blood vessels. By binding to VEGF, bevacizumab blocks VEGF binding to its receptors. Since it's launch in January 2005 bevacizumab has become the standard of care for 1st line mCRC in the vast majority of developed countries.

In June 2007, NICE recommended in TA118 that bevacizumab should not be added to first-line chemotherapy of metastatic colorectal cancer with 5-FU plus FA+/- irinotecan. Whilst the Appraisal Committee acknowledged the clinical benefits of bevacizumab (median increase of 4.7 months OS when adding bevacizumab to 5-FU plus FA + irinotecan) they had concerns over the cost-effectiveness of its use, which was estimated to result in a cost per QALY of £62,857 when bevacizumab was added to 5-FU plus FA + irinotecan.

The most recent update to the bevacizumab marketing authorization for CRC (January 2008), based upon the NO16966 phase III RCT, is now less prescriptive in the combination therapies bevacizumab may be combined with. Consequently the licence now states *"Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum".* This represents a new bevacizumab based intervention for CRC patients, with a different profile of costs and outcomes and therefore requiring a new economic evaluation and assessment. The Avastin patient access scheme (APAS) has been designed so that bevacizumab in combination with oxaliplatin-based regimens meets NICE's criteria for cost-effectiveness when compared to current best practice in the UK.

1.3. Please state whether the patient access scheme is financially based or outcome based

The Avastin Patient Access Scheme (APAS) is categorised as a financially based scheme and is designed to reduce the total cost of using bevacizumab in combination with oxaliplatin-based chemotherapy.

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

The APAS applies to mCRC patients who are suitable for treatment with bevacizumab in combination with oxaliplatin-based chemotherapy and that have not been previously treated for mCRC.

1.5. Please provide details of when the scheme will apply to the population specified in 1.4. Is the patient access scheme dependent on certain criteria (for example, degree of response, response by a certain time point, number of injections)? If so:

The scheme will apply to all eligible patients who are suitable for treatment as described in 1.4.

• Why have the criteria been chosen?

Not applicable.

• Please also give details of how the criteria are measured and the reasons for choosing these measures.

Not applicable.

1.6. What proportion of the population specified in 1.4 is expected to meet the scheme criteria specified in 1.5?

Not applicable.

1.7. Please explain how the NHS will be rebated through the patient access scheme.

There are four elements to the APAS:

- bevacizumab will be charged at a fixed price per treatment cycle
- after 12 claimed months of treatment a patient will receive free of charge bevacizumab for the remaining duration of first line treatment
- oxaliplatin will be provided free of charge through the scheme.
- a one-off upfront payment made for each patients commencing treatment

Fixed price per cycle

The APAS is based on a fixed price per cycle of treatment as opposed to a price per vial.

Bevacizumab will be purchased through normal channels from Roche (i.e. at the NHS list price per vial) .

Having received APAS usage data from the hospital pharmacy based on the submission of individual patient treatment forms, Roche will calculate the difference between the purchase price of vials used and the agreed fixed treatment cost per cycle. This will ensure that the same fixed price is charged for all patients and all cycles Any rebate will be provided as a credit note, free of charge stock or a cash alternative depending on the local preferences of each NHS Trust.

12 month cap

After 12 months of claimed treatment, all subsequent use of bevacizumab will be reimbursed in full at the NHS list price through the remaining treatment period, i.e. up until disease progression.

Bevacizumab will be purchased as normal from Roche and rebated in full by the provision of a credit note, free of charge stock or a cash alternative depending on the local preferences of each NHS Trust.

The APAS scheme will still be applicable and available should clinicians choose to use an intermittent treatment of oxaliplatin-based chemotherapy plus bevacizumab. The APAS would be applicable regardless of treatment breaks so long as patients are restarted on oxaliplatin-based treatment.

For the avoidance of doubt, the 12 month cap will relate to 12 cumulative months of treatment and not 12 calendar months, therefore treatment breaks will be accounted for within the APAS should patients be treated intermittently.

If a patient is transferred to an alternative chemotherapy regimen this would signify the start of second line therapy and thus they would no longer qualify for the APAS, as bevacizumab will not be recommended for second line therapy. This definition was suggested by the experts attending the advisory board with respect to intermittent treatment for patients in the UK.

Oxaliplatin

Oxaliplatin will be provided free of charge to patients enrolled in the APAS for the entire duration of first line treatment with bevacizumab.

Upfront Payment

The trust will receive a one-off payment of [redacted] for each patient registered on APAS that commences treatment with bevacizumab.

1.8. Please provide details of how the scheme will be administered. Please specify any additional data or information that may need to be collected, explaining when this will be done and by whom.

The APAS will utilise an electronic communication system to minimise the burden of administration to NHS Trusts.

Registration on to a web based APAS will take place once Roche has received a signed contract from an NHS Trust to participate in the scheme.

Whilst web based ordering form would be the preferred method of registration onto the scheme, we will also offer an alternative fax-back and paper based system in instances where the web based system may not be accessible. These forms would be faxed or posted back to Roche either individually or in batches depending on the preference of the Trust.

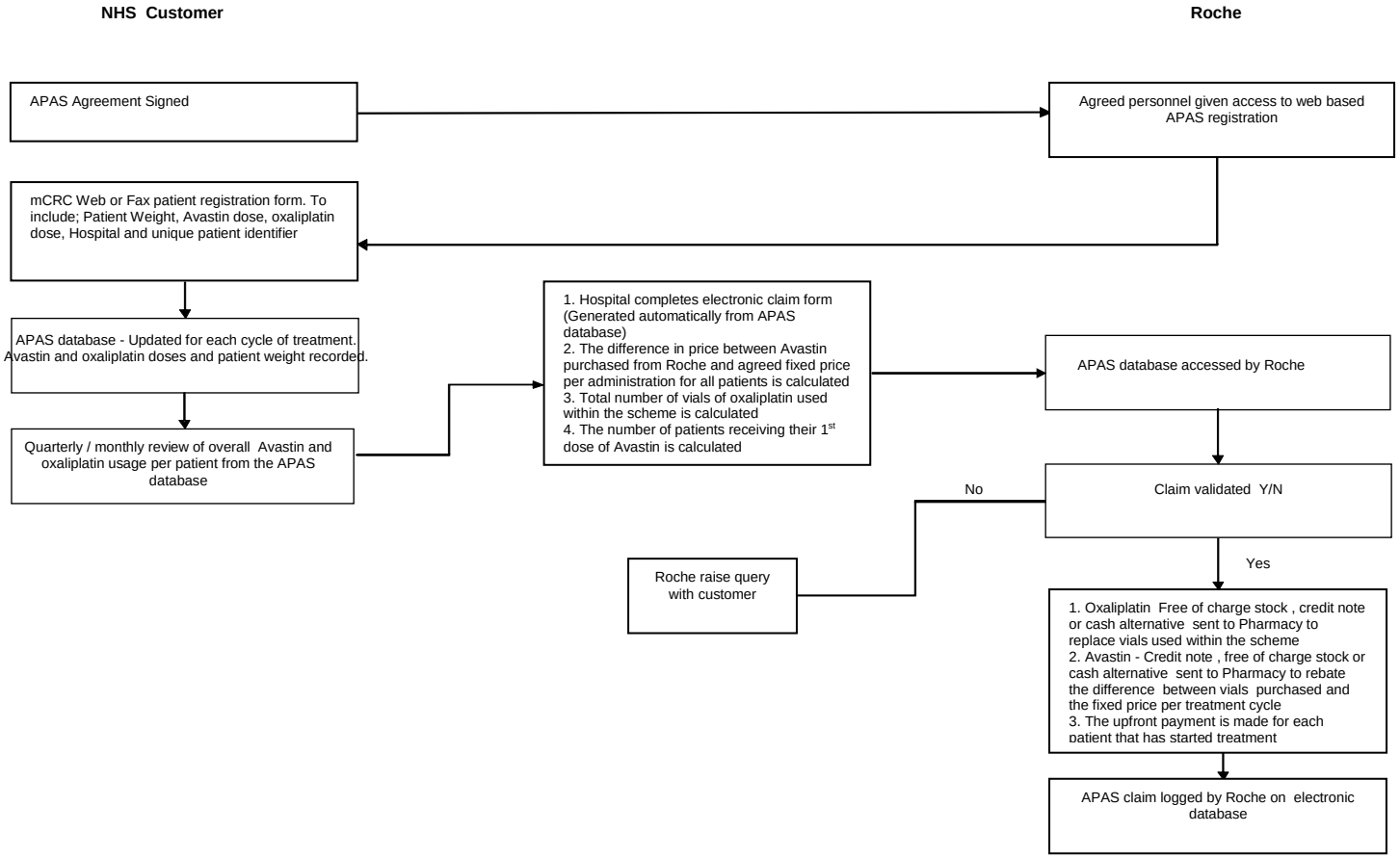
The APAS database will require the entry of a minimum registration dataset per patient so that the scheme can be appropriately governed and administered. Such data collection will be fully compliant with the requirements of the Data Protection Act and other relevant legislation.

The APAS database will be accessed by each Trust's appointed scheme administrator(s) (e.g. oncology pharmacist). The database (web or fax–back) can be updated with each cycle of treatment, monthly or quarterly depending on local preferences.

All patient data will be anonymised. The database will automatically calculate the rebate on each patient's treatment and an electronic claim will be generated either monthly or quarterly.

Once claims have been verified by Roche, a credit note, free of charge stock, or a cash alternative will be issued against the usage of Avastin and oxaliplatin depending on the preference of the NHS Trust. This will occur within 30 days of receiving the APAS usage data.

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



1.10. Please provide details of the duration of the scheme.

The APAS will remain in place until NICE re-review bevacizumab for the treatment of 1st line mCRC. After any re-review the scheme may be withdrawn or modified or carry on in its current form depending upon the outcome of any re-appraisal. In any case and in line with best practice, Roche would provide a formal notice period to NHS Trusts regarding any proposed changes to the scheme following any NICE re-review.

1.11. Are there any equity or equalities issues relating to the patient access scheme bearing in mind current legislation and any issues identified during the course of the appraisal? If so, how have these been addressed?

No equity issues have been identified.

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

The APAS web based access and database software is currently in development. We attach in the appendix to this submission the current draft of the registration fax-back form.

The electronic system in terms of functionality is similar to software already in use for other approved patient access schemes.

2 Cost effectiveness

2.1 Methodological approach

2.1.1 Please provide details of how the patient access scheme has been incorporated into the economic analysis.

Fixed Price

The fixed price per cycle for bevacizumab has been multiplied by the average number of cycles per month observed in the pivotal trial. This monthly cost has then be applied to each model cycle (for 12 months, see below) for the 1st line treatment health state (PFS_T).

12 month price cap

In the APAS, patients do not pay for treatment beyond 12 months. Hence the monthly cost for bevacizumab is only applied to the first 12 monthly model cycles in the PFS_T health state.

Free of charge oxaliplatin

The cost of oxaliplatin in the bevacizumab arms of the model have been set to zero.

Up-Front Payment

[redacted] has been removed from the cumulating drug acquisition cost of bevacizumab.

2.1.2 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. Please provide details of how this has been done. No other changes should be made to the model.

The results presented in the cost effectiveness section below are based on the revised base case as described in Roche's response to the ACD.

2.1.3 Please provide details of any additional patient-related costs incurred by implementing the patient access scheme (see table 1). The costs should be provided for the intervention with and without the patient access scheme.

The are no additional "patient-related" costs associated with APAS.

Table 1 Patient-related costs for the intervention with and without the patient access scheme.

	Intervention without PAS		Intervention with PAS	
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**
Intervention acquisition				
Monitoring tests				
Diagnostic tests				
Appointments				
Other costs				
Total patient-related costs				

**2.1.4 Please use table 2 to list any operational costs related to the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). Please give the reference source of these costs. Please refer to section 6.2 of the 'Specification for manufacturer/sponsor submission of evidence' [*currently reference is made to sections in the draft for external consultation December 2008* www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/singletechnologyappraisalsprocess/reviewofthespecificationformanufacturersponsorsubmissionofevidence.jsp *; this will be updated with the final version on publication]*).

Table 2: Resource consumption per patient by frequency of activity

Activity Frequency	Person Minutes per patient*	Source
Initial Set-up Activities	20	Total per trust / cumulative patients per trust over years 1-3
Ongoing Monthly Activities	41	Total per month / average prevalence of patients in a trust * the average number of months a patient remains on APAS
Per Patient Activities (One-off per patient)	25	Total as per estimated in Appendix A
Every Cycle	45 XELOX 66 FOLFOX	Per cycle time * number of bevacizumab treatment cycles estimated by economic model
Total	131 XELOX 152 FOLFOX	

* The difference between FOLFOX and XELOX arises due to the difference in cycle duration (every 2 and every 3 weeks respectively) between the regimens.

The estimated time per patient of administering the APAS was 131 minutes and 152 minutes per patient for XELOX and FOLFOX based regimens respectively.

The unit cost per minute for each of the professionals conducting the activities was calculated based on the mid-point salaries taken from the 2009 Agenda for Change pay scales combined with the overhead and salary on-costs taken from the PSSRU (PSSRU, 2008). Since overhead estimates for all the professionals involved were not available, overheads for these professional were assumed be the same as for a hospital pharmacist. As per assumed in the PSSRU, the calculation of unit costs per hour were based on 1565 working hours in a year. The resulting unit costs are shown in the table 3 below.

Based on the above, the cost per patient of operating the APAS over years 1 to 3 is estimated to be £57 and £67 for B-XELOX and B-FOLFOX respectively. (calculations provided in appendix).

For more details on the estimation the cost per patient please refer Roche's response to the ACD.

2.2 Summary results

Base-case analysis

2.2.1 Please present the cost-effectiveness results as follows:

• Table 4 should summarise the results for the intervention without the patient access scheme

• Table 5 should summarise the results for the intervention with the patient access scheme.

Table 4 Base-case cost-effectiveness results without patient access.

	B-FOLFOX-4	B-FOLFOX-6	B-XELOX	XELOX	FOLFOX-6	FOLFOX-4	FOLFIRI mdg	FOLFIRI dg
Intervention acquisition cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost difference (£):								
B-XELOX intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-6 intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-4 intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£)								
B-XELOX intervention	N/A	N/A	N/A	**104,870**	54,941	37,869	58,625	39,482
B-FOLFOX-6 intervention	N/A	N/A	N/A	158,195	**108,267**	91,194	96,313	77,171
B-FOLFOX-4 intervention	N/A	N/A	N/A	176,091	126,163	109,090	108,962	89,819

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

Table 5 Base-case cost-effectiveness results with patient access scheme.

	B-FOLFOX-4	B-FOLFOX-6	B-XELOX	XELOX	FOLFOX-6	FOLFOX-4	FOLFIRI mdg	FOLFIRI dg
Intervention acquisition cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost difference (£):								
B-XELOX intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-6 intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-4 intervention	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£)								
B-XELOX intervention	N/A	N/A	N/A	**29,975**	Dominant	Dominant	5,692	Dominant
B-FOLFOX-6 intervention	N/A	N/A	N/A	74,532	**24,604**	7,531	37,183	18,041
B-FOLFOX-4 intervention	N/A	N/A	N/A	107,189	57,260	40,188	60,264	41,121

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

2.2.2 Please present the incremental results as follows:

• Table 6 should summarise the results without the patient access scheme

• Table 7 should summarise the results 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.

Table 6 Base-case incremental results without patient access scheme.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
FOLFIRI mdg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
FOLFIRI dg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
B-XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£104,870	£104,870
B-FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£158,195	Ex-Dominated
B-FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£176,091	Ex-Dominated

Table 7 Base-case incremental results with patient access scheme.

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
FOLFIRI mdg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
B-XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,975	£29,975
FOLFIRI dg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Dominated
B-FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,532	Ex-Dominated
B-FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£107,189	Ex-Dominated

2.2.7 Please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses (see table 8). 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.

Impact of patient access scheme on ICERs

In section 4.14 of the ACD, the Committee noted that it was not clear how the three components of the patient access scheme contributed to the reduction in the ICER. The table below illustrates how the ICER changes with each additional element of the APAS

Cumulative changes	**ICER (£000's)**	
	B-XELOX vs XELOX	**B-FOLFOX-6 vs FOLFOX-6**
Base Case without APAS	105	108
12 month price cap	[redacted]	[redacted]
Oxaliplatin FOC	[redacted]	[redacted]
Fixed Price per Cycle	[redacted]	[redacted]
Up Front Payment	30	25

3 Appendices

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

DRAFT FAX BACK FORM.

[redacted]

Operating cost of APAS

[redacted]

APAS administration cost calculations

[redacted]