NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

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

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

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

2 Instructions for manufacturers and sponsors

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

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

Please refer to the following documents when completing the template:

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

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

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

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

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

When making a patient access scheme submission, include:

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

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

3 Details of the patient access scheme

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

Name of the technology:*	Tocilizumab (RoActemra™)
Disease area for which the proposed patient access scheme applies:	Moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. RoActemra can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or in combination with MTX.
*Please detail all names which apply and include all trading names.	

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

The PAS was originally designed in relation to the currently ongoing rapid review of TA 198 for tocilizumab in adult rheumatoid arthritis (RA). Issues and rationale particular to this appraisal can be found in Roche's relevant submission for the TA198 rapid review.

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

This qualifies as a simple discount.

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:

The scheme applies to all populations for which tocilizumab has EMA marketing authorisation in both RA and sJIA indications.

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:

The scheme will apply to all sales of tocilizumab after the date of final guidance publication.

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

The PAS is relevant to the whole license for tocilizumab, which includes adult RA and systematic juvenile idiopathic arthritis (sJIA). The scheme is a simple discount and consequently will not be subject to limitation within specific disease sub-types.

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

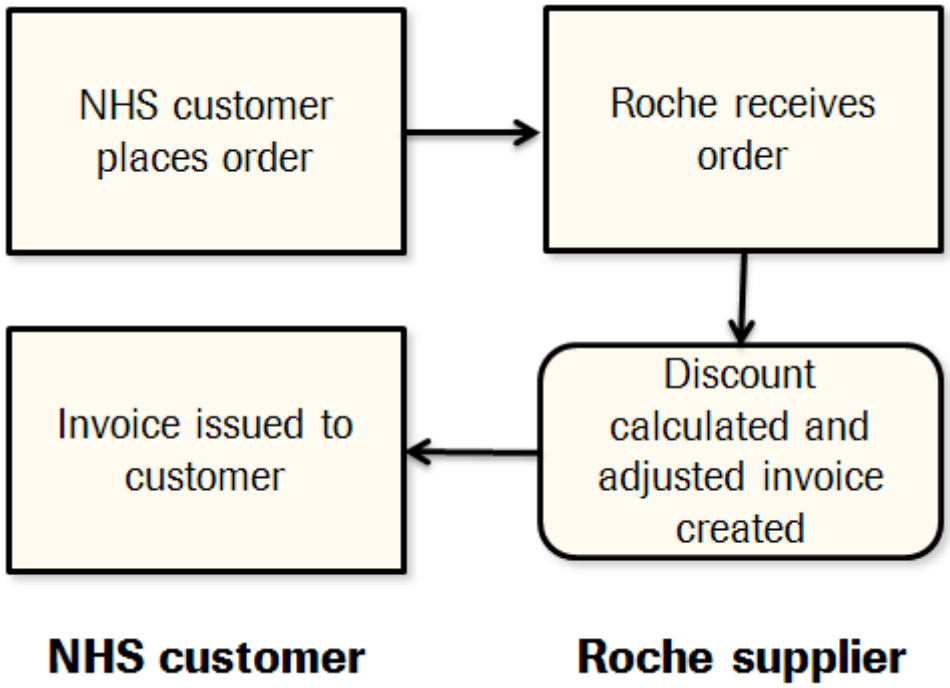
The PAS is a simple discount scheme [redacted]. The discount will be applied through adjustments to invoices rather than a reduction in drug list price [redacted]

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.

The discount will be applied through adjustments to invoices rather than a reduction in drug list price

[redacted] No additional administration is required to qualify for the scheme. NHS customers and purchasing pharmacists will need to be notified of the discount level which will remain confidential in NICE and DH documents. This approach has been adapted for other patient access schemes, e.g. azacitidine for the treatment of myelodysplastic syndromes.

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



Please note that all payment and funding arrangements may remain unchanged.

3.10 Please provide details of the duration of the scheme.

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

In any case and in line with best practice, Roche would provide a formal notice period of a minimum of 6 months to NHS Trusts regarding any proposed changes to the scheme following any NICE guidance 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?

None.

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.

None required.

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.

N/A

4 Cost effectiveness

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

The scheme applies to all licensed populations for tocilizumab.

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.

In the economic model incorporating the PAS, we have adjusted the individual vial prices to reflect the discount applied to tocilizumab.

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

The clinical data are best represented by the American College of Rheumatology (ACR) response rates in the pivotal TENDER trial and the trials

of comparator medicines estimated by indirect comparison analysis for methotrexate-inadequate responding (MTX-IR) pateints. These are provided in Table 1. The table also shows the relative risks estimated from the indirect comparison analysis. These statistics are the same as those used in the initial manufacturer submission except that the TENDER dataset has been restricted to only include the 95% of patients who had a prior exposure to MTX.

Table 1. ACR rates used in economic model

Treatment	ACR response category	Proportion attaining
Anakinra (not including 'no fever' outcome)		
	ACR 30	0.420465116
	ACR 50	0.394883721
	ACR 70	0.305335974
	ACR 90	0.124971582
Anakinra (including 'no fever' outcome)		
	ACR 30	0.487931034
	ACR 50	0.458244965
	ACR 70	0.377282957
	ACR 90	0.199706286
Infliximab ('no fever' outcome not available)		
	ACR 30	0.259121805
	ACR 50	0.112452953
	ACR 70	0.088291491
	ACR 90	0.046735124
Tocilizumab (not including 'no fever' outcome)		
	ACR 30	0.904
	ACR 50	0.849
	ACR 70	0.699
	ACR 90	0.37
Tocilizumab (including 'no fever' outcome)		
	ACR 30	0.849
	ACR 50	0.797346239
	ACR 70	0.656472345
	ACR 90	0.347488938
	Relative risks	
Tocilizumab vs. Anakinra (- 'No fever')		2.15
Tocilizumab vs. Anakinra (+ 'No fever')		1.74
Tocilizumab vs. Infliximab (ACR 30)		2.63
Tocilizumab vs. Infliximab (ACR 50)		4.88
Tocilizumab vs. Infliximab (ACR 70)		4.22

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'

Implementation of this PAS is not expected to be associated with any additional administration costs to the NHS.

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.

As this is a financial scheme, we do not expect any change in clinical management costs.

Summary results

Base-case analysis

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

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

Results of the revised base-case model with and without PAS are shown in Table 2. The PAS substantially improves the base-case cost effectiveness with an ICER of £16,262 per QALY gained compared to anakinra.

Table 2. Base-case cost-effectiveness results

	A	TA	TA with PAS
Total costs (£)	£136,871.46	£165,321.05	[redacted]
Difference in total costs (£)		£28,449.59	[redacted]
QALYs	3.3700	4.3310	4.3310
QALY difference	-	0.9609	0.9609

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

ICER (£)		£29,606.23	£16,923.01

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio; A = anakinra, T = tocilizumab.

Abbreviations used in treatment sequences: A: anakinra; T: tocilizumab.

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

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

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

Given the information request in the Appraisal Consultation Document (ACD) we will present incremental results which estimate the costs and benefits of the following sequences of treatment:

1. anakinra alone (A)
2. infliximab alone (I)
3. infliximab followed by anakinra (IA)
4. infliximab followed by tocilizumab (IT)
5. tocilizumab followed by infliximab (TI)
6. tocilizumab followed by anakinra (TA)

The comparisons carried out as part of this 'incremental analysis' do not match exactly the conventions set out for incremental analysis defined in this question. Rather, they match the information request posed by the Appraisal Committee in section 1.2 of the ACD.

Table 3. Base case incremental results without PAS applied

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)	Comparison
I	114,593.33	2.7709				
IA	127,802.55	3.6062				
A	136,871.46	3.3700	9,068.91	-0.2361	Dominated	vs. IA

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

IT	139,674.57	3.3848	25,081.24	0.6139	40,855.96**	vs. I
TI	151,439.61	4.1262	36,846.28	1.3553	27,186.60	vs. I
TA	165,321.05	4.3310	37,518.50	0.7248	51,765.09	vs. IA

Table 4. Base case incremental analysis results with PAS applied

Treatment sequence	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY gained)	Comparison
I	£114,593.33	2.7709				
IA	£127,802.55	3.6062				
A	£136,871.46	3.3700	£9,068.91	-0.2361	Dominated	vs. IA
IT	[redacted]	3.3848	[redacted]	0.6139	£30,629.57	vs. I
TI	[redacted]	4.1262	[redacted]	1.3553	£18,194.05	vs. I
TA	[redacted]	4.3310	[redacted]	0.7248	£34,949.43	vs. IA

We have also created a fully incremental analysis with the PAS applied, as per instructions for this question. However, for the comparisons required in this appraisal we feel that Table 3 and Table 4 provide a set of comparisons which are more appropriate to the appraisal at hand.

The fully incremental analysis Table 5 suggests that the tocilizumab strategies involving infliximab are either dominant over, or cost-effective compared to anakinra alone, however for the most high-cost strategy, tocilizumab followed by anakinra, the incremental ICER compared to the preceding tocilizumab→infliximab strategy is in excess of £30,000 per QALY gained. As the last three lines of the analysis involve costs and QALYs estimated in combination tocilizumab strategies for which no direct clinical evidence is available, interpretation of these results should be approached with due caution.

Table 5. Fully incremental analysis with PAS applied

Treatment Strategy	Total cost (£)	Total QALYs	ICER versus baseline	Incremental Costs (£)	Incremental QALYs	ICER (incremental)
I	114,593.33	2.771				
IA	127,802.55	3.606	15,813.72	13209.22	0.84	15,813.72
A	136,871.46	3.370	37,182.74	9068.91	-0.24	Dominated
IT	[redacted]	3.385	30,629.57	[redacted]	0.01	Dominant
TI	[redacted]	4.126	18,194.05	[redacted]	0.74	7,897.39
TA	[redacted]	4.331	24,703.78	[redacted]	0.20	67,788.72

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.

In light of our current ACD consultation response, we have presented the sensitivity and scenario analyses requested in ACD section 1.2, with the PAS included. These may be compared with the same analyses (without a PAS applied) provided in our ACD response.

Table 6. Results assuming increase of the adjustment factors by 30%

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£112,068.97	2.9051				
A	£136,871.46	3.3700				
TI	[redacted]	4.1894	[redacted]	1.2843	£20,240.04	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	£16,923.01	vs. A

Table 7. Assume decrease of the adjustment factors by 30%

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£117,031.11	2.6404				
A	£136,871.46	3.3700				
TI	[redacted]	4.0647	[redacted]	1.4243	£16,406.71	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	£16,923.01	vs. A

Table 8. . Results assuming stopping rule after two years

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£114,593.33	2.7709				
A	£136,871.46	3.3700				
TI	[redacted]	4.1262	[redacted]	1.3553	Dominant	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	Dominant	vs. A

Table 9. Results assuming administration every four weeks after the first six months

Treatment Sequence	Total cost	Total QALYs	Inc. Cost	Inc. QALYs	ICER	Comparison
I	£114,593.33	2.7709				
A	£136,871.46	3.3700				
TI	[redacted]	4.1262	[redacted]	1.3553	Dominant	vs. I
TA	[redacted]	4.3310	[redacted]	0.9609	Dominant	vs. A

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

As this new model involves patient-level simulation but few additional sources of variability, there is little to be gained from a PSA at present. A PSA could be provided on request.

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

Please see response to 4.9.

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.

N/A

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.

Please see previous responses.

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 as this is a simple discount PAS with a confidentiality arrangement.

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.

Response

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.

Response

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.

Response

5.1.5 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).

Response

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

Response

5.1.7 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.

Response

5.1.8 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.

Response

5.1.9 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.

5.1.10 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.