[redacted]

National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

27th October 2011

Dear [redacted],

Re. Appraisal Consultation Document (ACD) for Tocilizumab for the treatment of rheumatoid arthritis (RA) (rapid review of technology appraisal guidance 198)

MSD welcomes the opportunity to comment on the ACD for tocilizumab for the treatment of RA. Our comments are outlined below.

MSD is concerned that the wording and layout of the advice in the ACD could result in inappropriate use of tocilizumab.

The ACD states that: *"Tocilizumab in combination with methotrexate (MTX) is recommended as an option for the treatment of RA…if:*
…it is used as described for ***other*** *tumour necrosis factor (TNF) inhibitor treatments"*

This statement can easily be misinterpreted and may lead the reader to believe that tocilizumab is a tumour necrosis factor (TNF) inhibitor which of course it is not. Tocilizumab is a humanised monoclonal antibody against the interleukin-6 receptor (IL-6R). It is not a TNF inhibitor treatment and thus should not be grouped together with this class.

Advice for tocilizumab should align clearly to licensed indications.

Tocilizumab is licensed for use in combination with methotrexate (MTX) for the treatment of RA in patients who have responded inadequately to or were intolerant to previous therapy with one or more DMARD OR tumour necrosis factor (TNF) inhibitor treatments.

Tocilizumab can be given as monotherapy in patients who are intolerant to MTX, or where continued treatment with MTX is inappropriate.

By separating the advice for tocilizumab across sections 1.1, 1.2 and 1.3 of the ACD, MSD believe that the licensed indications for tocilizumab may, inadvertently, be misrepresented. We would suggest that sections 1.1 and 1.2 should be combined so that advice is given for patients who responded inadequately to one or more DMARDs or TNF inhibitor treatments. It should be made clear that tocilizumab is not a TNF inhibitor treatment, and thus should be prescribed after inadequate response to one or more DMARD or TNF inhibitor treatments. This is in line with licence.

Treatment pathway and sequential use.

Currently there is clear NICE guidance on the options available for patients who have experienced an inadequate response to a TNF inhibitor as a first line biologic. TA195 states that:

"Rituximab in combination with methotrexate is still recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, ***including at least one TNF inhibitor.*** *Additional treatment options are now recommended for these adults if rituximab therapy is contraindicated or withdrawn because of an adverse event, specifically:*

- *If rituximab is contraindicated or withdrawn, adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are now recommended as treatment options.*
- *If rituximab therapy cannot be given because methotrexate is contraindicated or withdrawn because of an adverse event, adalimumab and etanercept, each as monotherapy, are now recommended as treatment options"*

This wording has also been incorporated into TA225 (appraisal of golimumab) and TA186 (appraisal of certolizumab).

However, there is no guidance on the treatment pathway if a non-TNF inhibitor is used as the first line biologic, nor are there any trials where efficacy of biologics used second line after an IL-6 inhibitor currently available.

It is currently unclear what impact a recommendation for tocilizumab as a first line biologic therapy would have on the treatment pathway. By recommending tocilizumab as a first line biologic the committee are requiring rheumatologists to take a prescribing decision with no evidence base and to assume that if patients fail tocilizumab, an alternative biologic will be effective and safe.

Consideration of all costs and relevant cost data within the submission and Patient Access Scheme (PAS).

Central to the PAS supplied by Roche is the idea that the discount of [redacted] "*aims to equalize drug acquisition costs between etanercept and tocilizumab".*

This statement leads to a number of questions regarding the applicability of the discount in its proposed form and the validity of the figures used by Roche to achieve price parity with etanercept.

Derivation of the annual cost of tocilizumab.

There is inconsistency and a lack of clarity around how tocilizumab is costed within the PAS. Figure 1 from the PAS shows an annual cost of [redacted] for tocilizumab and an annual administration cost of [redacted]. However, from table 1 below, it can be seen that for a 70 kg patient the annual drug cost based on MIMS October prices, and assuming the least possible wastage (best case for tocilizumab) less [redacted] discount, would be [redacted].

Adding a [redacted] administration cost results in an annual cost (including discount) of [redacted] per patient. As stated in the PAS, etanercept has an

annual cost of £9,295 and thus this discount does not provide price parity with etanercept as is claimed.

Applicability of a defined discount for weight based pricing

As stated above, the PAS and economic modelling for the tocilizumab submission relies on a single patient weight of 70 kg. Whilst we acknowledge that NICE has taken this approach in previous assessments of infliximab within Rheumatoid Arthritis (TA130 and TA195), MSD would suggest that aggregated costs are a more suitable method for costing technologies where price is dependant on weight.

By assuming a patient weight of 70 kg and applying the [redacted] discount, price parity with etanercept is almost achieved (see above) for tocilizumab. However, by fixing the discount irrespective of the weight of the patient the NHS could stand to face a much larger budget impact than expected. Referring to Table 1 below, it can be seen that for any patient who weighs over 70 kg, even when the discount is applied, price parity with etanercept (the most expensive of the subcutaneous TNF inhibitor treatments) is not achieved.

Table 1 – Calculation of weight based costing of Tocilizumab (TOCI)

Weight	Number of Vials per infusion (assuming least wastage)	Cost of TOCI per infusion	Cost of TOCI per year	Cost of TOCI per year less discount	Admin cost per year	Total cost	Total cost less discount
[redacted]							

From the BSRBR registry data on infliximab it can be seen that of all monitored patients treated with infliximab, [redacted] weigh over 70 kg.

From Table 1 it can be demonstrated that the NHS could face costs of up to [redacted] per patient per year. In the DMARD experienced population (where tocilizumab is currently not recommended) the NICE costing statement for TA225 (appraisal of golimumab for the treatment of RA) states that approximately 34,600 patients are eligible for treatment with a biologic agent. The use of tocilizumab in such a large population where an estimated [redacted] weigh over 70 kg could create a large budgetary impact for the NHS.

Taking the weight distributions for infliximab from the BSRBR database and applying the discount to the cost of tocilizumab it can be seen that the aggregated cost per patient per year would be likely to be £11,276. This is much greater than the cost of the TNF inhibitor treatments and suggests that the proposed discount does not work as described. For the calculations used to derive this figure please see table 2 below.

Table 2 – Calculation of aggregated cost per patient per year of tocilizumab

	Weight group (Kg)				
	0-33	**34-66**	**67-100**	**101-133**	**>133**
infliximab patients per BSRB weight group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients in each weight category	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per tocilizumab infusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per tocilizumab infusion less discount	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
tocilizumab infusions per annum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
tocilizumab cost per patient per weight group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per weight group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
tocilizumab Administration cost per patient per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total tocilizumab admin cost per weight group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total tocilizumab cost per weight group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total tocilizumab cost per patient per weight group	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Therefore expected tocilizumab cost per patient per year is equal to:	(number of patients*total cost 0-33 kg group*percentage of patients in 0-33 kg group)+(number of patients*total cost 34-66 kg group*percentage of patients in 34-66 kg group)+(number of patients*total cost 67-100 kg group*percentage of patients in 67-100 kg group)+(number of patients*total cost 101-133 kg group*percentage of patients in 101-133 kg group)+(number of patients*total cost >133 kg group*percentage of patients in >133 kg group)				
Which equates to:	[redacted] **= £11,276.26**				

The opportunity cost to the NHS

MSD consulted with a number of clinical and specialist rheumatology nurses to advise on the potential impact of providing infusion services every 4 weeks. The consensus was that infusion services are currently operating either at or near to capacity, so if the NHS is required to provide infusion services every 4 weeks the resource required will need to be deployed from elsewhere. If these resources are moved from providing more cost-effective services, the NHS will not be maximizing possible QALY gains and will have the opportunity cost of the lost alternative services imposed upon it.

Additional costs of treatment with tocilizumab

Prior to initiating treatment with tocilizumab, blood tests are required to check for liver enzyme abnormalities and absolute neutrophil count in all indicated populations.

Section 4.4 of the tocilizumab SmPC also states that liver enzymes should be monitored every four to eight weeks for the first six months of treatment, followed by every twelve weeks thereafter. In JIA they should be measured after the second infusion and then thereafter according to good clinical practice. These tests are not required for infliximab (Remicade) or golimumab (Simponi). MSD would ask whether the associated costs of these tests and subsequent workup for abnormal values have been taken into account.

The SmPC for tocilizumab states that:

" …assessment of lipid parameters should be performed four to eight weeks following initiation of therapy with tocilizumab…

During the six month controlled trials, increases of lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol have been reported commonly. With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to 4.1 mmol/ l. Elevations in lipid parameters responded to treatment with lipid-lowering agents.

During the double-blind controlled period and with long-term exposure, the pattern and incidence of elevations in lipid parameters remained consistent with what was seen in the 6-month controlled trials".

These elevations in lipid parameters are likely to mean significant additional treatment costs for patients prescribed tocilizumab, especially as the SmPC suggests that these patients should all be treated with lipid lowering drugs. MSD would query whether the associated costs have been taken into account.

Although this population isn't within any NICE guidelines, patients with RA are at increased risk of CVD. In light of the lack of clear data, any increases in lipids need to be considered or carefully monitored.[1,2].

In addition, section 3.14 of the ACD states that:

" The manufacturer reported that…adverse events reported more frequently with tocilizumab 8 mg/kg monotherapy than in the methotrexate group were abdominal pain and discomfort, headache, dizziness, rash, pruritis and elevated blood pressure, neutropenia, leukopenia and hyperlipidaemia. Most of these events were mild and transient."

MSD would challenge the use of the phrase "mild and transient" with respect to lipid elevations as this is in direct contradiction to the SmPC. The SmPC for tocilizumab states that:

"With routine laboratory monitoring it was seen that approximately 24% of patients receiving RoActemra in clinical trials experienced sustained elevations in total cholesterol ≥ 6.2 mmol/ l, with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/ l"

The committee should also note that complications of diverticulitis and GI perforation are specifically mentioned in the SmPC for tocilizumab (sections 4.4 and 4.8).

Medium term safety data for the TNF inhibitor treatments.

Since TA198, the established TNF inhibitor treatments, infliximab, etanercept, and adalimumab have accumulated a significant amount of medium term safety data which has been collected and published by the BSRBR. In addition, there is considerable long-term clinical trial safety data for the established TNF inhibitors. At this time no medium term safety data is available for tocilizumab.

In conclusion MSD has concerns around the content, wording and layout of the advice in the ACD. This could potentially result in inappropriate use of tocilizumab for the treatment of patients with RA.

If you require any further information or clarification around any of the points we have raised, please do not hesitate to contact me.

Yours Sincerely,

[redacted]

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[1] D H Solomon, N J Goodson, J N Katz, M E Weinblatt, J Avorn, S Setoguchi, C Canning, S Schneeweiss *Patterns of cardiovascular risk in rheumatoid arthritis*Ann Rheum Dis (2006) 65:1608–1612

[2] Christophe Meunea, Emmanuel Touzéb, Ludovic Trinquartc, Yannick Allanored *High risk of clinical cardiovascular events inrheumatoid arthritis: Levels of associations of myocardial infarction and stroke through a systematic review and meta-analysis* Archives of Cardiovascular Disease (2010) 103: 253—261