Multiple Technology Appraisal (MTA)

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDS or after conventional DMARDS only have failed [ID537].

Appraisal consultation document (ACD)

Napp Pharmaceuticals Limited

Redacted Version 170715

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Dear Meindert

Thank you for the opportunity to comment on the draft final guidance on the use of TNF alpha-inhibitors in Rheumatoid Arthritis [ID537]: Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDS or after conventional DMARDS only have failed.

Comments on changes to the draft scope

NICE has asked stakeholders if they would like to comment on the inclusion of the biosimilar infliximab (Remsima and Inflectra,) as an additional intervention in the scope and matrix of this multiple technology appraisal.

Napp Pharmaceuticals Limited are naturally delighted that NICE has included Remsima®, into the draft scope. We were also pleased to be able to attend the last committee meeting on May 21st.

NICE has recognised that the inclusion of Remsima represents an opportunity for the NHS to acquire infliximab at a much lower price. The lower price not only improves, obviously, the cost-effectiveness of this intervention but also allows the NHS to make savings which can be used to improve patient care. This could allow more patients to be treated with anti-TNF alpha inhibitors or to allow funding of alternative treatments either existing or innovative new medicines. We believe that NICE has a role to play in providing clarity with respect to the value of biosimilars, which we believe is something that local commissioners and clinicians are looking for to help local decision making. This may improve uptake and therefore help realise the opportunities highlighted above.

The Appraisal Committee request for comments

We note from the consultation document that The Appraisal Committee is interested in receiving comments on the following:

- **Has all of the relevant evidence been taken into account?**
- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

We believe that there has been every attempt to take the evidence into account. However we note that there have been concerns raised about the use of a cut-off point for the disease activity score (DAS28) score of 5.1 Clinicians and patient groups have suggested that some patients may have a lower DAS score yet have persistent synovitis, and may do badly if not treated early enough with TNF-alpha inhibitors. Patients may experience pain, disability and loss of function that may not have been picked up in scoring systems yet contribute to a substantial loss of quality of life and potential societal costs. These patients may benefit from the use of TNF-alpha inhibitors before a DAS score of 5.1 is reached. Indeed we believe from reading the ACD that The Committee not only understands this but is empathetic to this situation. We would hope that it will be able to find a pragmatic approach to dealing with the somewhat arbitrary cut-off point of 5.1.

We would support a more flexible approach to patient selection that would allow those patients classified as having moderate to severely active disease access to these medicines provided they have had prior treatment with conventional DMARD therapy. This would allow the clinicians the opportunity to apply their judgement and use a trial of TNF-alpha inhibitor treatment with close monitoring and within the confines of a “stopping-rule.”

Comments on the preliminary recommendations.

1.1 and **1.4**

We note with interest that The Committee has recommended **(1.4)** that the lowest price medicine should be used where appropriate and with the provisos as stated.

We support this view however, we would like to suggest that NICE finds a way to sign post stakeholders, particularly payers and prescribers, to the lower acquisition prices possible through the procurement tender process. This could be done as a footnote to recommendation **1.4** or as an extra bullet point in **1.1**.

For the latter we would suggest:

- and that the companies supplying biosimilar infliximab (Remsima and Inflectra) should at least maintain the agreed discounted procurement prices.

2.4

We suggest that the phrase “more recently,” is slightly an inaccurate statement as these biological medicines were introduced more than 10 years ago,

3.1

After the sentence “A biosimilar medicine is a medicine that is developed to be similar to an existing biological medicine”.

Please consider inserting: In line with European Medicines Agency (EMA) requirements, biosimilars undergo an extensive comparability exercise to demonstrate that they have comparable physicochemical properties and biological activity as the originator product.

3.11

We suggest that it would be useful to clarify that the indication for infliximab (both Remicade and the biosimilars Remsima and Inflectra) is identical.

For example:
Infliximab biosimilars (Remsima, Napp Pharmaceuticals and Inflectra, Hospira UK), in combination with methotrexate, have precisely the same UK marketing authorisations as Remicade, namely for the reduction of signs and symptoms as well as the improvement in physical function in adults with active disease when the response to DMARDs, including methotrexate, has been inadequate……..

3.12

We note that NICE refers to net price when referring to the cost of medicines. This is factually incorrect as it is the NHS list price. In the case of the Remsima this would be the *gross* price and the net price would be the true acquisition price through the negotiated tender prices which will be at least [redacted] and up to [redacted] lower than the NHS list price for Remicade.

We suggest revising the text to read

The NHS list price of infliximab biosimilars is £377.66 per 100-mg vial (information provided by the companies). Assuming a weight per person of 70 kg, no vial wastage, and 3 initial doses in the first year followed by treatment every 8 weeks, the cost in the first year is £6344.69, and then £5155.06 per year. Actual acquisition costs may vary significantly in different settings because of negotiated procurement discount.

We would also like to point out that infusion costs vary by hospital and if given as home infusions the treatment is VAT exempt.

4.2.43

We note that the Assessment Group (AG) has taken into account all patient access schemes. The AG may not have considered the lower acquisition costs associated with Remsima through the tender process. We are however conscious that this would not have changed the preliminary recommendation of The Committee which includes infliximab as a treatment option. Including the tender price would only serve to reinforce the value of infliximab biosimilars to the NHS.

The average administration cost per subcutaneous injection of £3.05 seems very low. Did the AG take into account the costs of patient education, nurse support and clinic visits for those biologics administered subcutaneously rather than simply consider that such patients were not carefully monitored (which comes at a cost)?

4.2.75

The AG has carried out an analysis using the NHS list price for Remsima and Inflectra, infliximab biosimilars, which has had the effect of reducing the ICER by approximately 7%. We would suggest that in future appraisals that tender prices could be used in a sensitivity analysis as this would have a greater effect on the ICER. The Committee mentioned that the NHS list price was *only* 10% lower than the originator infliximab whereas the negotiated tender prices will be at least [redacted] and up to [redacted] lower than the originator (Remicade) NHS list price. This would have a considerable effect on the ICER.

4.3.5

We note that The Committee has recognised the issues for people with a DAS score of below 5.1 or those who have contra-indications to conventional DMARDS. The Committee also recognised the clinical interest in the use of biological DMARDS for people with moderate disease. It is disappointing that The Committee was unable to make a recommendation for this group of people that would allow them access to the use of biological DMARDS, we would like to suggest that further consideration should be given to the criteria that would allow access to these life changing treatments.

4.3.10

The Committee may not be aware of the potential NHS savings that could be made by switching from originator infliximab to biosimilar infliximab. Furthermore The Committee should be made aware of the active switch programmes and recent policy changes relating to the use of biosimilars in other countries such as Australia[1], Finland[2] and The Netherlands[3]. We would suggest that statements such as: *"However, if a person is already on a treatment and their disease is responding, they would not be switched to a biosimilar*" could hinder uptake of biosimilars in the UK. This opinion is not universally held within the UK clinical community, and a number of centres are already actively switching RA patients from originator to biosimilar infliximab[4]. Furthermore this opinion is not based on robust scientific evidence, as the EMA has authorised biosimilar infliximab as having no clinically relevant difference to originator infliximab[5]. In Norway 62% of patients are now being treated with Remsima, which includes a significant number of switch patients from originator to the significantly less expensive biosimilar[6].

In the extension phase of the PLANETRA rheumatoid arthritis study patients treated with Remicade up to week 54 were allowed to switch to Remsima and were followed for up to 102 weeks. There were no reported significant differences in response or side-effects.

We wish to point out that the use of subcutaneous injections of do not obviate the need for other costs. There are costs associated with education, support and clinical reviews of these patients on subcutaneous doses rather than intravenous infusions where problems are picked up sooner avoiding extra hospital clinic visits.

We wish to reiterate that the NHS list price is not indicative of the true acquisition price of Remsima in the UK. We are therefore disappointed to see comments such as "…was only 10% less…"and "….only a small reduction in in the ICER…." We would reiterate our point made earlier that commissioners and clinicians are looking to bodies such as NICE and MHRA to provide clarity on this topic at this time.

In reality the true acquisition price for biosimilars through the procurement tender process is substantially lower at [redacted] below the originator list price of £419.62; which would in turn lead to a much lower ICER than that quoted.

4.3.18

The AG's exploratory analysis in sections 4.2.74 - 4.2.75 incorporated the price of the biosimilars and The Committee noted that this did not alter the base case ICERs substantially. We contend that the AG should have used the negotiated tender prices which will be at least [redacted] and up to [redacted] lower than the list price for Remicade £419.62 which we suggest would have altered the ICER more significantly.

4.3.22

We would like to understand whether the ICERs quoted in this section were calculated using only list prices or whether PAS where appropriate for some products and tender prices for the biosimilars were included. Home therapy infusions could also have a saving of 20% by being VAT exempt.

We are disappointed that those patients with moderate disease but with fast HAQ progression are still being denied access to biological DMARDS on the basis of a QALY of £28,500. We would suggest this is likely to be lower if the true price for the biosimilars had been included.

Summary of Conclusions Table

<u>The Committee's recommendations:</u>

We suggest a minor amendment to this sentence beginning: "Start treatment with……." so that it reads:

Start treatment with the least expensive drug (taking into account: local acquisition discounts, administration costs, dose needed and product price per dose).

<u>Evidence for cost-effectiveness.</u>

Most likely cost-effectiveness estimate (given as an ICER)

The Committee concluded that biological DMARDs were a cost-effective use of NHS resources only for people with severe active rheumatoid arthritis previously treated with methotrexate.

For people with moderate active disease previously treated with methotrexate and with severe active disease not previously treated with methotrexate It concluded that biological DMARDs were not cost effective.
They also could not be considered as a cost-effective use of NHS resources when used as monotherapy.

Whilst we agree with the first point above, we do not agree that the current suggestion of a cut-off point for the DAS score of 5.1 is fair to all patients with moderate disease. We also feel that recognising the lower tender prices as the true acquisition costs of biosimilar infliximab projects more realistic conclusions about which medicine option should be taken for NHS patients.

Table Section 4 page 72

Additional factors taken into account		
Patient access schemes (PPRS)	Four patient access schemes were taken into account, for tocilizumab, abatacept, golimumab and certolizumab pegol.	4.2.43
End-of-life considerations	None	–
Equalities considerations and social value judgements	There were no equality issues raised during the Committee discussion.	4.3.25

We believe that the use of PPRS is inappropriate here and may have the potential to mislead the reader that the rebates being paid by the Pharmaceutical Industry are being taken into account in health economic evaluations.

We suggest the following amended table should be used:

Additional factors taken into account		
Patient access schemes (PAS)	Four patient access schemes were taken into account, for tocilizumab, abatacept, golimumab and certolizumab pegol.	4.2.43
Biosimilar acquisition prices	Only the NHS list price was used not the NHS tender acquisition price	4.3.10
End-of-life considerations	None	–
Equalities considerations and social value judgements	There were no equality issues raised during the Committee discussion.	4.3.25

5.4

We note with interest that the agreement between the DH and companies offering patient access schemes has been mentioned.

We suggest that NICE considers adding a comment here to reflect that the biosimilars are also available to the NHS at substantial discounts below the NHS list price.

5.5

Implementation support tools are a recognised part of NICE guidance. It would be useful if examples in the costing template could reflect a range of prices for biosimilars rather than only include calculations based purely on NHS list price.

We hope that you find our comments and suggestions useful. Should you have any questions arising from this response please contact me in the first instance?

Yours sincerely

[redacted]

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