Multiple Technology Appraisal (MTA)

TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis (including a review of TA143 and TA233) [ID694]

Appraisal consultation document (ACD)

Napp Pharmaceuticals Limited

Redacted Version

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Dear Meindert

Thank you for the opportunity to comment on the ACD for the above mentioned MTA, we have a number of points that we would like to bring to the attention of The Committee.

Napp Pharmaceuticals Limited are disappointed to read that The Committee has recommended that NICE should exclude infliximab from the list of approved TNF-alpha inhibitors in its guidance for the treatment of ankylosing spondylitis (AS).

We were present at the committee meeting on February 25th and believe that patient representatives made a strong case to include intravenous infliximab as an alternative for those patients not wishing to use or who are unable to use sub-cutaneous medicines. In section 4.25 of the ACD the patient groups went on to suggest a group of people who might benefit from an infusion and in fairness, disadvantages were also discussed.

It is clear from The Committee papers and the consultation document that infliximab offers people with AS an option which in clinical trials has demonstrated a rapid and yet sustained reduction in symptoms as measured by BASDAI and BASFI scores similar to other anti-TNFs. In fact in section 4.8 "*the Assessment Group (AG) noted that the results for infliximab at 10-16 weeks appeared slightly better than results for the other TNF-alpha inhibitors (although the credible intervals are wide)."*

In section 4.9 "*the AG concluded that the long-term benefit of TNF-alpha inhibitors appear similar across treatments"*.

Although patients see a value in having an alternative delivery route to the other 4 interventions The Committee concluded (Section 4.71) it could not recommend the use of infliximab simply on the basis of another treatment choice.

This would suggest that infliximab is not being excluded due to clinical reasons but primarily on grounds of cost-effectiveness. The Committee noted that the ICERs for infliximab were higher than the other TNF-alpha inhibitors and concluded that the ICERs for infliximab were not within the range considered to be a cost-effective use of NHS resources. The Committee suggested that this was largely due to the higher administration costs. We can demonstrate that there is no one infusion cost that can be quoted reliably and the variation is such that the Assessment Group for the recent RA MTA applied a different cost for infusions to that used in this appraisal in fact it was nearly half of that used here: £154 vs £291. Furthermore by using the list price rather than the true (i.e. local procurement tender) NHS acquisition price for the biosimilar infliximab the guidance is biased against the biosimilar versions of infliximab.

We suggest that there are two parts to this problem:

- the first is that NICE does not seem to have a mechanism within the methodology for dealing with tender prices as the agreements are not national and may not be concluded at the time of appraisal

- and the second is how to differentiate the lower cost and therefore more cost-effective Remsima® biosimilar infliximab from the originator in the NICE guidance.

This is obviously an unforeseen problem that has arisen since NICE published its position paper on biosimilars. http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/biosimilars-statement.pdf. Point (*e)* in the position statement says that *"The Department of Health in England has confirmed that a technology remit referred to NICE enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market".* Unfortunately this has not taken into account the potential effect of the significantly lower price and how this affects the ICER leading to the need to differentiate the more cost-effective biosimilar.

When calculating the cost effectiveness of infliximab the AG has used the NHS list prices for infliximab whether for the originator or biosimilar versions. (£419.62 for 100mg Remicade®, MSD and £377.66 for Remsima, Napp Pharmaceuticals Limited). This results in ICERs that do not reflect the true cost to the NHS as infliximab is subject to the tendering process.

The AG were able to demonstrate that by using the lower published NHS acquisition price the ICER for biosimilar infliximab, Remsima, is lower than that of the originator Remicade. However as the real acquisition price is subject to the tendering process it has not been possible for the AG to look at the effect that tender pricing has on the ICER.

AG ICERs	Rebound to Baseline	Rebound to Natural history
Infliximab	£ 40,576	£ 66,529
Remsima	£ 36,751	£ 60,222

We have applied a range of lower tender prices and varying infusion costs to the executable model in order to test its accuracy. We present our findings in the tables below. We show for comparison Tables 8 and 9 from the ACD. We are unable to calculate the Rebound to Baseline ICERs as we do not have a model for this; however we would suggest that the ICERs for Remsima would be similar to the other TNF-alpha inhibitors.

Table 8. Base case results for ankylosing spondylitis: rebound to baseline

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	110,821	7.245	-	-	-
Golimumab	130,173	8.163	19,352	0.918	21,079
Adalimumab	130,257	8.163	19,436	0.918	21,170
Etanercept	130,630	8.163	19,810	0.918	21,577
Certolizumab	132,059	8.163	21,238	0.918	23,133
Infliximab	148,073	8.163	37,252	0.918	40,576
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

The ICER for Remsima biosimilar infliximab at list price is calculated by the AG to be £36,751

Table 9. Base case results for ankylosing spondylitis: rebound to natural history

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	109,933	7.265	-	-	-
Golimumab	131,960	7.867	22,027	0.603	36,554
Adalimumab	132,045	7.867	22,111	0.603	36,695
Etanercept	132,423	7.867	22,489	0.603	37,322
Certolizumab	133,851	7.867	23,918	0.603	39,693
Infliximab	150,022	7.867	40,088	0.603	66,529
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

The ICER for Remsima biosimilar infliximab at list price is calculated by the AG to be £60,222

From the executable model we tested the assumption that the ICER was sensitive to infusion cost and to the cost of infliximab. We noted that the AG used a body weight of 73kg for its calculations. We also note that in the executable model it was assumed that all patients using injectable TNF-alpha inhibitors were able to give the treatment themselves and no nursing or follow up home or GP appointments were assumed.

Using the executable model for *Rebound to Natural History* we have produced deterministic ICERs for Remsima compared to conventional therapy for 3 different infusion costs (£187[1], £291[2] and £314[1]. The ICERs range from best case [redacted] to the worst case (highest cost and highest infusion cost) [redacted]. (Please see Table 1 A to C). Note that there appears to be considerable variability in the published infusion costs from as low as £107 to £314[1].

1 National Schedule of Reference Costs - Year 2013-14 - NHS trusts and NHS foundation trusts – CHEMOTHERAPY

2 AG executable model referenced to TA143

Table 1 Scenario A **Infusion cost £291 as per AG**

Remsima Price (£)	Strategy	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
	Conventional Therapy	7.231		106,486		
	Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Golimumab	7.835	0.605	128,669	22,183	36,681
	Adalimumab	7.835	0.605	128,754	22,267	36,821
	Etanercept	7.835	0.605	129,132	22,645	37,447
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
377.66	Remsima	7.835	0.605	143,100	36,614	60,545
	Infliximab	7.835	0.605	146,747	40,261	66,576

Scenario B **Infusion cost as per 2013 tariff** **other** **£187**

Remsima Price (£)	Strategy	Mean QALYs	Inc QALYs	Mean Costs	Inc Costs	ICER
	Conventional Therapy	7.231		106,486		
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Golimumab	7.835	0.605	128,669	22,183	36,681
	Adalimumab	7.835	0.605	128,754	22,267	36,821
	Etanercept	7.835	0.605	129,132	22,645	37,447
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
377.66	Remsima	7.835	0.605	140,840	34,354	56,808
	Infliximab	7.835	0.605	144,487	38,001	62,839

Scenario C	Infusion cost as per 2013 tariff			o/patients	£314	
Remsima Price (£)	**Strategy**	**Mean QALYs**	**Inc QALYs**	**Mean Costs**	**Inc Costs**	**ICER**
	Conventional Therapy	7.231		106,486		
	Certolizumab Pegol PAS	7.835	0.605	126,987	20,500	33,900
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Golimumab	7.835	0.605	128,669	22,183	36,681
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
	Adalimumab	7.835	0.605	128,754	22,267	36,821
	Etanercept	7.835	0.605	129,132	22,645	37,447
	Certolizumab Pegol	7.835	0.605	130,560	24,074	39,809
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
[redacted]	Remsima	7.835	0.605	[redacted]	[redacted]	[redacted]
377.66	Remsima	7.835	0.605	143,600	37,113	61,371
	Infliximab	7.835	0.605	147,247	40,761	67,402

Published NHS list price in blue

In scenario A using the infusion cost of £291.00 from the AG's model Remsima (priced at example tender prices of [redacted]) is more cost-effective than certolizumab without a PAS (ICER [redacted] vs 39,809) and is within the range of all of the other TNF-alpha inhibitors (£33,900 to £39,809) except for the originator infliximab (Remicade) which has an ICER of £66,576.

In scenario B where there is a lower infusion cost of £187.00 (based on the chemotherapy infusion cost) the range of ICERs for the tender price range of [redacted] falls to [redacted] to [redacted]. In fact at the lowest two (post tender) prices Remsima is the most cost-effective of all the TNF-alpha inhibitors. In this scenario Remsima falls below or well within the range of ICERs for the other TNF-alpha inhibitors (£33,900 to £39809) except for the originator infliximab (Remicade) which has an ICER of £62,839.

In scenario C we have used the highest cost infusion of £314.00. The ICERs for the other TNF-alpha inhibitors range from £33,900 to £39,809. At the tender price range of [redacted] the ICERS for Remsima range from [redacted] to [redacted]. This would yet again make Remsima an equally cost-effective alternative for treating AS. However the originator infliximab (Remicade) has an ICER of £67,402.

We understand how, when using NHS list prices it has been possible for the committee to give a recommendation on the use of infliximab however this would remove patient access to this valuable biologic medicine.

We recommend strongly that the committee re-examine this decision taking into account the discounted tender prices and how given the greater cost-effectiveness of Remsima it is possible to make this valuable biologic medicine more available to people with AS.

We have summarised the ICERS for the different Remsima tender price ranges (Table 2) and included the infusion cost ranges. The resultant ICERs are comparable to the other TNF-alpha inhibitors and are similar to those calculated by the AG in Table 9.

Table 2 Summary ICERs Rebound to natural history

	Infusion cost	Infliximab Cost per 100mg	ICER Range		ICERS AG Table 9*
Remsima	£187 to £314	[redacted]	[redacted]	[redacted]	**
Remsima (AG infusion cost)	£291	[redacted]	[redacted]		**
Certolizumab Pegol PAS		-	£ 33,900		**
Golimumab		-	£ 36,681		£ 36,554
Adalimumab		-	£ 36,821		£ 36,695
Etanercept		-	£ 37,447		£ 37,322
Certolizumab Pegol		-	£ 39,809		£ 39,693
Remsima	£187 to £314	[redacted]	[redacted]	[redacted]	**
Remsima	£187 to £314	£377.66***	£ 56,808	£ 61,371	£ 60,222
Infliximab (Remicade)	£187 to £314	£419.62***	£ 62,839	£ 67,402	£ 66,529

* Base-case ICERS Rebound to Natural History Table 9 ACD ** ICER Not calculated by AG *** NHS List Price

Recently the ACD for RA MTA has been circulated for consultation. In the section on Cost of Interventions (4.2.43) it states that; *"In the absence of robust data the Assessment Group used an infusion cost of £154 and a time of 1 hour from the NICE technology appraisal guidance on tocilizumab"*

If we were to apply this infusion cost to the AS MTA model it would again support the use of Remsima as it has the effect of lowering the ICERs for Remsima even further as in Table 3 below.

Table 3 Summary ICERs Rebound to natural history applying RA infusion cost of £154

	Infusion cost	Cost per 100mg	ICER Range		ICERS AG Table 9*
Remsima	£ 154	[redacted]	[redacted]	[redacted]	**
Certolizumab Pegol PAS			£ 33,900		**
Golimumab			£ 36,681		£ 36,554
Adalimumab			£ 36,821		£ 36,695
Etanercept			£ 37,447		£ 37,322
Certolizumab Pegol			£ 39,809		£ 39,693
Remsima	£ 154	[redacted]	[redacted]		**
Remsima NHS list price	£ 154	£ 377.66***	£ 55,622		£60,222
Infliximab (Remicade)	£ 154	£ 419.62***	£ 61,653		£66,529

* Base-case ICERS Rebound to Natural History Table 9 ACD ** ICER Not calculated by AG

*** NHS List Price

We believe that this clearly demonstrates the difficulty of evaluating the cost-effectiveness of infliximab. By ruling infliximab out of the options available to clinicians the NHS will lose the opportunity to use biosimilar infliximab instead of the originator brand. Furthermore this limits patients' choice to only subcutaneous injectable TNF-alpha inhibitors.

It has been suggested to us by health economists from academic units used for technology appraisals that a way forward would be for Napp to offer a confidential Patient Access Scheme (PAS). We have explored this, and believe that unlike new chemical entities (NCEs) where a discount through a PAS is used to effectively lower the ICER to an acceptable level, it would not be possible to have a PAS and the tender process running simultaneously as this would only lead to confusion for payers.

We know from previous examples that prices reduce over time and this would make the biosimilars even more cost-effective. The biosimilar market is somewhat similar to a generic market where there is more competition and prices are subject to fluctuation.

We are aware that NICE currently is unable to include a national tender price as there are a number of tenders across NHS England. We have demonstrated above that Remsima is cost-effective when compared to conventional therapy.

More biosimilar medicines will soon be available and it is likely that they will be subject to the tender process. NICE may wish to consider how it can handle the discrepancy between the actual price paid by the NHS and NHS list price so that the real actual acquisition price can be included to avoid any confusion in its guidance.

Would it be possible for NICE to consider how it could issue guidance such that CCG's and NHS Trusts could be advised to use infliximab provided it is acquired below a set price £x per 100mg vial? An alternative would be to state that *infliximab is recommended but only at or below the prices agreed within the regional procurement prices.*

We estimate that there are approximately 485 patients with AS who would be eligible for infliximab.

In summary we urge NICE to reconsider how it calculates the ICERs for medicines that are subject to the tendering process. The current process by only considering published NHS list price is clearly biased against the biosimilars. On this occasion the draft advice is denying patients access to a much lower cost product which we have demonstrated to be cost-effective within the range that is acceptable for the comparator products.

We hope that The Committee will be able to review its decision based on the cost-effectiveness of Remsima (biosimilar infliximab) as demonstrated here and allow infliximab as an alternative treatment for AS patients.

If you have any questions relating to our response please contact me in the first instance.

Yours sincerely

[redacted]

[redacted]

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