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National Institute for Health and Care Excellence

Multiple Technology Appraisal

Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab, and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying anti-rheumatic drugs and after the failure of conventional disease-modifying anti-rheumatic drugs only

AbbVie's Response to the Appraisal Consultation Document

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Executive Summary

AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD).

We are pleased with the preliminary decision to recommend the biologic treatments for treating **severe** rheumatoid arthritis (RA) after the failure of conventional disease-modifying antirheumatic drugs (cDMARDs). We are however disappointed that those patients with **moderate** RA will not have the same access to biologic treatments that have shown to be highly effective in improving functional impairment and patient outcomes. AbbVie believes that patients with moderate RA should not be disadvantaged by preventing them access to optimal care through a decision made by the Committee based on an ICER obtained from methodology that has certain limitations.

The positive recommendation for biologics in severe RA is based on an ICER the Committee considered to likely lie between £41,600/QALY and £25,300/QALY, whereas the negative recommendation for in moderate RA is based on the base case ICER of £51,000. AbbVie believes that both the ICERs for severe and moderate RA in the appraisal are higher than they are in reality and that the decision has been made without adequately taking into consideration some of the relevant evidence. In **Section 1** we will therefore revisit the evidence that was provided and that AbbVie considered have not been fully taken into account. In particular:

1.1 **The change in quality life was inadequately captured in the appraisal, underestimating the health gain with biologics**
1.2 **Limited consideration was given to the interventions' value to society**
1.3 **Limited consideration was given to alternative discount rates allowed in the NICE Methods' Guide**

Due to the length of the appraisal process, additional published information has become available that has previously not been captured in the cost-effectiveness evaluation, namely:

1.4 **Value of adalimumab patient support programs to patients and the healthcare system**

As result of not fully taking into consideration all the evidence, AbbVie considers that not all the interpretations of the clinical and cost-effectiveness evidence were reasonable, which is particularly important to patients with moderate RA.

AbbVie also believes the ACD lacks clarification on a key issue, namely application of **the high responder subgroup in the moderate RA analyses to the moderate RA population,** and this is discussed in Section 2. We also request the Committee to reconsider the base case ICER for the moderate subgroup as there appears to be a **disconnect between the efficacy of biologics and the base case ICER in moderate patients** and a request to amend the ACD on the wording relating to **vial wastage for infliximab, biosimilar infliximab and tocilizumab.**

Therefore, whilst we welcome the positive recommendation for patients with severe RA, we do not believe that the provisional recommendations are sound or a suitable base for guidance to the NHS relating to moderate RA and we discuss the reasons for this in **Section 3.** In particular, biologic therapies have been available for RA in the UK since 1999 and have been recommended by NICE as early as 2002. As acknowledged in the ACD, biologic therapies such as adalimumab are considered as effective treatment options for people with moderate to severe RA who have failed conventional therapy and it was, and continues to be, innovative treatment in this population. Biologics are also widely reimbursed in major European countries for severe as well as moderate RA, with one publication noting that stricter treatment criteria seem to be associated not only with lower uptake of biologics, but also with higher disease activity, thus suggesting that principles of equitable heath care

systems might be undermined within Europe. Thus, not only does AbbVie consider it important for patients to have the opportunity to receive biologic therapies for this chronic, progressive and disabling disease, but AbbVie also believes that patients in the UK with moderate RA should have the opportunity to receive the same standard of care as in the rest of Europe. A possible solution would be to define a subgroup of moderate patients at highest risk of poor outcome.

Lastly, we would like to bring to the Committee's attention recent media reports based on the ACD that AbbVie believes misinterpreted the content of the ACD. We believe that amendments to the wording in the ACD may prevent future misunderstandings and we outline our suggested changes in **Appendix 1**.

To conclude, AbbVie considers that not all the benefits relating to biologics have been have been adequately captured and that the summaries of clinical and cost-effectiveness may not reflect the actual ICER of biologics, in particular moderate RA. We would like the Committee to further deliberate on the cost-effectiveness of biologics in moderate RA. We also propose amendments to the text relating to biosimilar products. Our detailed comments on these points are set out on the pages hereafter.

Section 1. Has all of the relevant evidence been taken into account?

1.1 Change in the quality of life has been inadequately captured, underestimating the health gain with biologics.

AbbVie considers that the changes in quality of life with biologic treatments were not adequately captured in this appraisal. We outline the reasons below.

1.1.1 Relationship between pain levels and HAQ scores

AbbVie welcomes the acknowledgement by the Assessment Group that they identified and corrected an error in their modelling following the feedback from AbbVie on the poor fit for the relationship between HAQ and pain.

However, it does not appear that the remainder of AbbVie's comments on the relationship between pain levels and HAQ scores were considered. To reiterate:

The data from the Research in Active Rheumatoid Arthritis (ReACT) study suggest that the impact of anti-TNF therapy on reducing pain may be underestimated in both the manufacturer and AG modelling, given that pain is not modelled independently from the modelling of HAQ improvement and is not considered to systematically differ between patients on different therapies. We illustrate this graphically below.

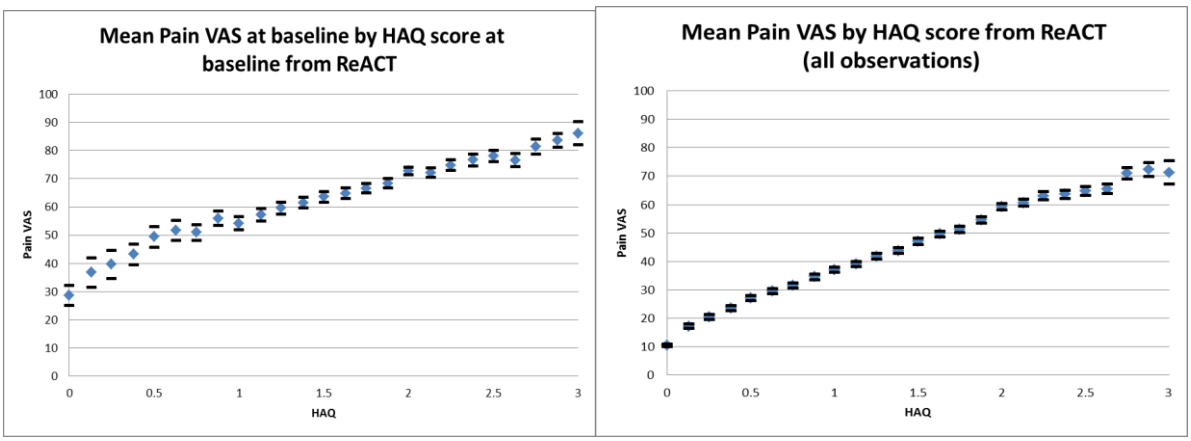

Figure 1. Mean Pain VAS relationship to HAQ score at baseline and for paired observations at all timepoints

These figures clearly show that the mean pain VAS is systematically higher at baseline compared to all levels of HAQ score when all observations are used (graph on the left vs. graph on the right). As the majority of patients at baseline (graph on the left) were on cDMARD therapy but had disease that was considered severe enough (DAS28>3.2) to require adalimumab therapy, they can be considered to be similar to patients in the appraisal who would continue on cDMARD, whereas patients on biologics are best represented by the graph on the right. It is hypothesised that the difference between the baseline and all observation data is attributable to the impact of adalimumab therapy on reducing the pain associated with RA. However, neither AbbVie nor the Assessment Group modelled different effects for the different treatment groups.

As result of not differentiating between cDMARDs and biologics, the benefits of biologics have not been fully captured in the Assessment Group model and AbbVie requests that the Committee take

this into consideration before making conclusions on the most appropriate the ICER for patients with moderate RA.

1.1.2 Psychological benefit of being in work

AbbVie notes comments sent to the Committee by the National Rheumatoid Arthritis Society (NRAS) highlight that patients consider it vital to stay in work not only for economic reasons, but also because of the psychological impact on patients: "*In a survey…. – 88 per cent of respondents said that having a job helped them cope with the disease with incidences of depression significantly higher among non-workers than workers"*[1].

AbbVie questions whether the emotional benefit of being able to return to work has been adequately captured in the methods used to calculate the QALYs and should the Committee consider this not to be the case, then the ICERs would be improved for the biologic treatments.

1.1.3 Risk of cardiovascular events among RA patients and benefits of biologic therapy

AbbVie would again like to highlight the cardiovascular (CV) benefit of biologic treatments in RA patients, a point also raised by the British Society of Rheumatology (BSR) during the appraisal, but which we do not think have been considered by the Committee.

A systematic review of the evidence on CV risk and management thereof prompted the European League Against Rheumatism (EULAR) to issue evidence-based recommendations for the CV risk management in RA. Amongst their findings were that the standardised mortality ratios are increased in RA patients and range from 1.5 to 1.9, with the increased risk of mortality in these patients mostly attributed to CV disease. These recommendations further note the necessity of early and effective control of disease activity to lower the CV risk in RA patients.[2]

Several studies have demonstrated the value of using anti-tumour necrosis factors (anti-TNFs) in risk reduction for CV disease among RA patients. A meta-analysis of 1,411 patients from four Phase II/III clinical trials of adalimumab (i.e., ARMADA, DE019, PREMIER, and OPTIMA) reported a 66% reduction in the hazard of major adverse CV events (MACEs) and 84% reduction in the hazard of nonfatal myocardial infarction among the adalimumab+MTX group compared to MTX monotherapy group[3]. In another example, a study using a large real-world registry evaluated the association between using anti-TNF therapy and risk of CV events (composite outcome of myocardial infarction, transient ischaemic attack or stroke and CV-related death) in 10,156 RA patients. This study reported a 61% hazard reduction in CV events among RA patients who used anti-TNFs compared to patients treated with cDMARDs.[4] Another study retrospectively examined 113,677 RA patients from the administrative claims database and reported use of anti-TNF therapy to significantly reduce the cumulative risk for any studied CV event (myocardial infarction, stroke, unstable angina, or congestive heart failure) by 21%, 38% and 51% over years 1, 2, and 3, respectively, compared to patients without anti-TNFs[5].

These benefits have not been adequately captured within the methodology employed by either the manufacturers or Assessment Group and as results may have underestimated the QALY gains of anti-TNFs. AbbVie requests that the Committee bear this in mind during their deliberations.

1.1.4 Changes in HAQ score can influence mortality

AbbVie welcomes the acknowledgement by the Assessment Group that if it can be proven that changes in HAQ did influence mortality, this would improve the cost-effectiveness of biologics.

To this effect, AbbVie would like to point out that in the publication used by the Assessment Group to determine relationship between HAQ and mortality; the authors reported that an improvement in HAQ of ≥0.5 units was associated with a significant reduction in mortality risk over all time-periods from six months through to three years. Similarly HAQ worsening was always associated with increased mortality risk.

More recently Ajeganova et al. investigated the relationship between disease activity (which has elsewhere been shown to be significantly correlated to HAQ[6, 7, 8, 9, 10]) over the first two and five years of RA and risk of mortality using the BARFOT cohort. They found that the hazard ratio for mortality for those with persistent disease activity was 1.7 times higher (1.1-2.4), and for those in intermittent remission 1.6 times higher (1.02-2.4) than for those in sustained remission. They concluded that persistent disease activity and intermittent remission during the first years after diagnosis of RA increased the risk of mortality independently of factors such as age, gender, smoking and treatment regimen.[11]

Thus there is evidence to suggest that changes in HAQ and disease activity affect mortality risk. As previously pointed out by AbbVie, the assumption used in the Assessment Group model that only baseline HAQ predicts mortality, may be a source of bias in the results as it ignores the effect of a more favourable HAQ progression for patients on biologics. This result in underestimation of additional survival provided by biologics over cDMARDs and AbbVie trusts the Committee will consider this relevant to the cost-effectiveness evaluation.

1.2 Limited consideration of the interventions' value to society

AbbVie welcomes the acknowledgement within the ACD that RA is associated with not only substantial direct costs, but also indirect costs such as reduced productivity (Section 2.1) and can have a significant effect on the lives of patients and their family (Section 4.3.1).

As the committee is aware, cost–utility analysis cannot be the sole basis for NICE's decisions and committees should use their judgement about the acceptability of an intervention as an effective use of NHS resources taking into account amongst others, the social value thereof.

Whilst AbbVie understands that benefits to society are not incorporated through the Institutes' reference case, which only considers the direct cost incurred by the NHS and benefits to the patients, AbbVie would still like to point out that no consideration was given to capturing the benefits of biologics on wider societal benefit through a scenario analysis in the Assessment Group model.

AbbVie therefore believes that the committee should give further consideration to the evidence regarding wider societal benefits which are presented below.

1.2.1 Indirect cost

The importance of work participation is also emphasised in the Treat-To-Target recommendations in RA, which suggest that participation in work is an integral part of the primary goal of treating RA patients.[12]

As also discussed in our submission and by the BSR and NRAS, there is an abundance of evidence of the effects of RA on the wider costs to society, and in particular, work participation. This evidence shows that the cost of sick leave due to work related disability is substantial and that many patients are forced to leave employment due to their disease. Loss of productivity and high absenteeism due to the debilitating effect of RA has indirect costs to society, as does other costs such as caring for a

family member or friend with RA and costs incurred by patients purchasing aids and devices to assist with reduced mobility caused by RA. The relative importance of these costs with respect to direct medical costs cannot be understated, and a report where these are not mentioned gives only a partial view of the true cost-effectiveness estimates of treatments.

For this reason AbbVie included in its submission sensitivity analyses which examined the effect of including costs due to the loss of work capacity. In these scenarios the ICER for moderate RA decrease by 36% (from £18,792/QALY to £11,964/QALY) and the ICER in the severe RA group by 35% (from £16,650/QALY to £10,905/QALY). Of note is that these analyses do not represent the entire spectrum of indirect costs incurred by patients with RA or wider societal costs, and thus incorporating additional societal costs such as cost to carers, state funded disability benefits and home adaptations will decrease the ICER even further.

Therefore, due to the importance of work participation and the considerable impact of indirect costs thereof, AbbVie requests that the Committee consider the value of biologics to society as part of their decision.

1.2.2. Non-clinical and non-cost benefits

It is unfortunate that the current NICE process cannot fully take into consideration some of the non-clinical and non-cost benefits associated with biologic treatments, but AbbVie would like to draw the Committee's attention to some of the benefits experienced by patients, as voiced through NRAS:

"Another aspect of the disease that is frequently overlooked is impact on the family. Our own research has found that when a person's partner has RA this is likely to have negative impacts for the person on: their domestic responsibilities; their employment choices and the family finances; their social life; their relationship with their partner including their sex life; and their own emotional wellbeing. Children with a parent who has RA are also likely to be affected by this into their adulthood."

Whilst these benefits cannot be directly quantified to the NHS, AbbVie would nonetheless call on the Committee to use their judgement about the acceptability of biologics as an effective use of NHS resources taking into account the non-clinical and non-cost benefits.

1.3 Limited consideration of alternative discount rates allowed by the NICE Methods Guide

AbbVie notes that the Committee considered the 3.5% discount rate to be in line with the current NICE Methods Guide (Section 4.3.1).

As the Committee would be aware, Section 6.2.19 of the NICE Methods Guide allows alternative discount rates to be considered *"in cases when treatments restore people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years."* and *"…if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved."*. The Methods Guide also goes on to state that *"…the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."*

Whilst the ACD states the Committee discussed that the discount rates were inconsistent between the original guidance and that they were aware of the economic rationale for equal discount rates for costs and benefits, it does not appear that the Committee considered alternative ICERs based on discount rates of 1.5% for costs and benefits as permitted in the Methods Guide. AbbVie understands

that this would not have been possible as the Assessment Group did not present a scenario using these discounts rates specifically.

The BSR in this appraisal has stated that the *"management of RA has been revolutionised by the introduction of biologic treatments"* and that biologics are *"highly effective"*[13]. Furthermore, they indicated that since the introduction of biologic therapies in 1999 there is *"…evidence of a reduction in inpatient treatment and orthopaedic surgery in patients with RA".*[14] NRAS echoes these points, stating that biologics *"…have been revolutionary in changing the way this disease is treated"*[15]*.* It is also noted in the ACD that patient experts have emphasised that biologics provided extensive benefits for people with RA and that the Committee themselves considers that *"biologics have significantly changed the management of rheumatoid arthritis"*

In light of the evidence on the impact of biologics on patient outcomes, AbbVie believes that the Method Guide recommendations for discount rates other than the base case 3.5% are plausible and requests that the Committee take this into consideration at the next appraisal meeting.

1.4 Value of adalimumab patient support programs to patients and healthcare system

AbbVie would like to highlight the value of adalimumab beyond the drug, which has currently not been captured in either of the Assessment Group report and manufacturer submission.

As stated in the AbbVie submission and subsequent consultations, AbbVie offers a free of cost patient support program (PSP) to adalimumab treated RA patients in the UK. The program includes elements such as homecare nurse visits, tailored self-management tools, telephone and online support for lifestyle and treatment advice.

A recent study (NCT01383421) compared the clinical and functional outcome of 852 RA patients in the EU, Mexico, Puerto Rico and Australia who initiated adalimumab and used AbbVie's PSPs with patients on adalimumab who did not use these programs. The study reported significantly better ($p<0.05$) improvements in clinical outcomes (DAS28-CRP: −2.88 vs. −2.13; SDAI: −30.57 vs −21.65; and CDAI: −26.98 vs −20.75) and trends towards higher proportion of patients achieving HAQ MCID change (73.8% vs. 67.2%), from baseline at week 52 among moderate to severe RA patients in favour of patients who initiated adalimumab and used PSPs.[16]

Another study conducted in a US setting using 2,386 patients reported a 22% reduction in disease-related medical costs and 10% reduction in total healthcare costs associated with utilisation of PSP among adalimumab treated patients compared to non-PSP patients.[17]

Thus, the value of the AbbVie PSP has not been captured in the cost-effectiveness evaluations and as early studies have shown, improves patient outcomes and lowers the cost of treatment. For this reason AbbVie considers that ICERs for both severe and moderate RA for adalimumab may be underestimated in this appraisal and we request that the Committee take this into consideration at the next appraisal consultation meeting.

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2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

Due to the reasons outlined in Section 1, AbbVie believes that the Committee may not reasonably have interpreted some elements of the clinical and cost-effectiveness evidence for biologics in this appraisal. We also question some of the statements and text within the ACD as detailed below.

2.1 Unclear justification for not considering the high responder subgroup in the moderate RA analyses

AbbVie notes that the Committee did not consider the sensitivity analyses for high responder patients in the moderate population plausible (Section 4.3.22), but do not offer an explanation for this in the ACD other than to state *"The Committee was not persuaded that the exploratory analysis for the moderate active group was as applicable to this group as to the severe active group".*

If, as the ACD states (Section 2.3.18), the Committee "*considered that such patients would be a subset of those currently having biological DMARDs and agreed it was appropriate to take this analysis into consideration when examining the most plausible ICER"* then this consideration should apply equally to the severe and moderate population.

Without understanding the reasons why the Committee did not consider this subgroup relevant to the RA population, consultees and commentators cannot fully address this point and AbbVie therefore requests clarification on the reasons why the high responder subgroup in the moderate RA analysis was not considered plausible by the Committee.

2.2 Disconnect between efficacy/effectiveness of biologics and base case ICER in moderate RA compared to severe RA

As noted in Table 3 in the ACD, patients with moderate and severe RA will have the same probabilities of responding to biologic treatment based on the network meta-analysis. These findings are supported by result from various registries (including those of the BSR) which indicate toward similar or better clinical benefits of initiating biologics in moderate disease activity compared to severe disease activity state[18,19,20]

On this basis it is difficult to understand how the Committee could reasonably interpret the base case ICER for moderate RA to be the most likely ICER when it is £10,000/QALY higher than the severe population. In contrast, when comparing the ICERs in the scenarios for the high responder subgroup one can see that they are very close: £25,300/QALY and £28,500/QALY. Similarly, in AbbVie's own submission, the difference in ICERs between moderate and severe RA patients were £2,000/QALY.

As there seems to be a disconnect between the efficacy of biologics (same efficacy) and the base case ICERs (£10,000/QALYdifference), AbbVie request that the Committee reconsider that the base case ICER for moderate RA is the most likely ICER for this group of patients. The more likely ICERs would be that of the high responder subgroups.

2.3 Query on the annual cost of infliximab, biosmilar infliximab and tocilizumab in the ACD

AbbVie has some concern regarding the ACD text in bold in the sections outlined below:

Section 3.10

> *… The net price of infliximab is £419.62 per 100-mg vial (BNF, April 2015). Assuming a weight per person of 70 kg**, no vial wastage** and 3 initial doses followed by treatment every 8 weeks, the cost in the first year is £7049.62, and then £5727.81 per year...*

Section 3.12

> *The net price of infliximab biosimilars is £377.66 per 100-mg vial 3.12(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…*

Section 3.31

> *.. The net price of tocilizumab is £102.40 per 4-ml (80-mg) vial, £256.00 per 10-ml (200-mg) vial, or £512.00 per 20-ml (400-mg) vial (BNF, April 2015). Assuming a weight per person of 70 kg, **no vial wastage**, and 13 doses per year, the annual cost (without the patient access scheme) of tocilizumab is £9318.40*

AbbVie queries whether it is appropriate to base the annual cost of infliximab, biosimilar infliximab and tocilizumab on the assumption that no vial wastage will take place. This is not an assumption that was made by any of the manufacturers or the Assessment Group in their cost-effectiveness calculations but most importantly, AbbVie understands that this is not commonly done in clinical practice and that it may not be considered acceptable due to the risk of contamination when keeping opened vials and sharing it between patients.

Additionally, the Summaries of Product Characteristics (SPC) for Inflectra and Remsima state: "Any unused portion of the infusion solution should not be stored for reuse". Similarly, for Remicade the SPC states "Do not store any unused portion of the infusion solution for reuse" and for tocilizumab "RoActemra is for single-use only".

AbbVie therefore requests that these sections be amended to reflect the annual cost based on <u>no</u> vial sharing, as in its current format it may be interpreted by the reader that the cost-effectiveness decision was made based on the cost of vial sharing.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Due to the points discussed previously AbbVie does not believe that for patients with **moderate** RA, the provisional recommendations are sound or a suitable basis for guidance to the NHS.

When first introduced, biologic therapies offered a step change therapy for people who have failed conventional therapy in moderate to severe RA. Indeed, it is now widely accepted that patients with persistent moderate and severe RA despite treatment with cDMARDs should be escalated to biologic therapy and this is reflected in treatment guidelines around the world from organisations such as the BSR,[21] EULAR[12], and the American College of Rheumatology[22]. We also note the Committee considered biologics and innovative class of drugs.

Not surprisingly therefore, **the use of these agents is standard of care across Europe and is also widely reimbursed in major European countries**. However, there are some striking and disconcerting findings in a cross-sectional study exploring access to biologics for RA patients among 46 European countries[23]. Crucially, among European countries where there is reimbursement for biologics their finding was that the UK was only 1 of 8 countries in Europe requiring a DAS score >5.1, while 18 had no DAS requirements or permitted biologics in moderate and severe disease, while 10 countries permitted biologics with a cut-off between 3.2-5.1. When exploring a composite score for clinical eligibility criteria to initiate a biologic, 4 countries had the maximum eligibility score (5 - most liberal), 12 countries had score 3 or 4 and 20 scored between 0 and 2 (most restricted). Countries from Eastern Europe and Former Soviet Union were more likely to be classified in the more restricted scores. It is notable that the UK was scored a 1 representing highly restricted access to biologics, and was the only western European country to be classified as having poor access. The authors also note that stricter clinical eligibility criteria seem to also be associated not only with lower uptake of biologics, but also with higher disease activity, thus suggesting that principles of equitable heath care systems might be undermined within Europe.

Additionally, AbbVie considers it is important for **patients with moderately active disease** to have the opportunity to receive biologics as those who fail biologic therapy **will still be left with the prospect of poor quality of life and/or becoming disabled as result of staying on failing treatment**. As emphasised in the BSR Guidelines[21] patients on aggressive cDMARD therapy including steroids may still have a DAS28<5.1 and yet still have very active disabling disease. Some of these patients may be corticosteroid dependent despite combinations of cDMARDs. Furthermore, corticosteroid use may reduce the DAS28<5.1, yet still not control disease satisfactorily. The NICE RA Management Guidelines recommend that attempts should be made to remove corticosteroids whenever possible, including the tactic of using biological drugs. It would be unethical to expect clinicians to withdraw therapies in these patients in an attempt to achieve the NICE criteria for access to biologic therapies as it would in effect precipitate a flare.

A possible solution to the concerns around the cost effectiveness of expanding access for biologics to patients with moderate disease activity would be to **define a subgroup at highest risk of poor outcome**. Factors associated with poor prognosis do not simply include a high DAS28 (a cut-off noted as arbitrary in the ACD), but also include other factors such as high baseline HAQ score, seropositivity, baseline radiographic damage and swollen joints. This is based on the EULAR recommendations which refer to earlier use of biologics in the presence of prognostically unfavourable factors such as early joint damage and rheumatoid factor (RF)/anti-citrullinated protein antibody (ACPA) positivity, whilst the ACR guidelines defines poor prognostic features as functional limitation, extra-articular disease, positive RF/ACPA and bony erosions by radiograph.[12,22]. In the BSR Guidelines on Eligibility for First Biological Therapy there is a requirement for demonstration of at

least three tender and swollen joints.[21] In their study using the ERAN database, Kiely et al. found that patients with a DAS of 4.2-5.1 had a worse outcome, and both HAQ and employment outcome were significantly worse, than those with a DAS 3.2-4.1, suggesting that this group may stand to gain the most from anti-TNF therapies[24]. The possibility of a subgroup of moderate patients for whom biologics are most appropriate is an area we hope the Committee can further explore with the clinical experts at the next appraisal meeting.

To conclude, on the basis that AbbVie believes that patients in the UK should receive the same standard of care as in the rest of Europe for a potentially disabling disease, we would urge the Committee to give due consideration to extending the availability of biologics to patients with moderate RA.

4. Are there any aspects of the recommendations that need particular consideration to ensure NICE avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

AbbVie has no comments on this point.

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Appendix 1

AbbVie wishes to bring to the Committee's attention that the provisional recommendations have been misinterpreted in recently published media articles,[25,26] particularly in reference to guidance on use of biosimilar infliximab, with implications that this biosimilar has preferential recommendation over the originator product and is also deemed as identical and therefore interchangeable with the originator.

Selected quotes include:

"As biosimilars are deemed to be identical to the reference product, companies are not asked to make new applications for the drug's appraisal by NICE."- attributed to a NICE spokesperson.

"The NICE spokesman says that this also means the draft guidance states: 'That treatment should be started with the least expensive drug'," – i.e. that biosimilar versions should be used ahead of Remicade in order to help the NHS save money."

In order to prevent further misinterpretation of the NICE position on biosimilars in future media reports and external publications, we recommend highlighting within Section 3 ("The technologies") the statement below in current and subsequent technology appraisals issued by NICE. This is would be critical to minimise inappropriate use of biological medicines.

> The NICE board paper item 06 on biosimilar technologies dated 19 Nov 2015, states in section 5: '*Biosimilars are different to generic drugs. Any guidance on biosimilars will use brand names as substitutability and interchangeability cannot be assumed, and ultimate decision making on biosimilars versus originator biologic must rest with the responsible clinician.*'[27]

It is also critical to highlight the MHRA drug safety updates issued in 2008[28] and 2012[29], which recommend all biological medicines including biosimilars are prescribed by brand name (not the INN) to avoid automatic substitution, and both brand name and batch number are recorded for adverse drug reactions. This will ensure product traceability and attribution of suspected adverse drug reactions to the correct product. Reiteration of the above in this technology appraisal will support rapid and accurate safety monitoring of RA patients prescribed a biological medicine, including biosimilars. This is also in line with the NICE board paper Section 4, referenced above.

Additionally, we have some proposed amendments to specific wording within the ACD:

Section 1.4 and Page 67, Key conclusion

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

This statement has been misquoted in the media as implying that NICE recommend that biosimilars should be used in place of the originator product. It is also not consistent with the wording used in a recent guidance issued for Ulcerative Colitis and the NICE position on biosimilars. In particular, the NICE board paper item 06 on biosimilar technologies in section 5 states: '*ultimate decision making on biosimilars versus originator biologic must rest with the responsible clinician.*'

AbbVie's suggestion would therefore be to amend the wording, thereby ensuring alignment with previously published statements, minimising ambiguity and providing clarity for the NHS, media and other parties who read the guidance.

As an example, using the wording from the NICE guidance on Ulcerative Colitis is provided below (TA329) would achieve this. The wording states:

"*The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose)."*

Section 3.1

> *"A biosimilar medicine is a medicine that is developed to be similar to an existing biological medicine."*

AbbVie request that the sentence be amended as follows (additional text underlined):

"A biosimilar medicine is a medicine that is developed to be similar to an existing biological medicine, <u>it is not identical."</u>

Section 3.1, Table 1

AbbVie would advise of the critical need to use the brand name in conjunction with INN to distinguish not just originators from their biosimilar versions, but also in future, between multiple biosimilars (from different manufacturers) of the same originator, reference product. These future biosimilar products (expected for infliximab and etanercept from 2016 onwards) will each be assessed on a case by case basis by the EMA and the resulting marketing authorisation for indication extrapolation may differ across the licensed indications available with the originator product. It is therefore critical to differentiate these products from one another in NICE technology appraisals.

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