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Dear Meindert,

MSD thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD). We welcome the Appraisal Committee's decision to recommend TNF-α inhibitors for ankylosing spondylitis (AS) and for non-radiographic axial spondyloarthritis (nr-ax SpA).

Our key concern is that the Appraisal Committee has decided not to permit 'switching' between TNF-α inhibitors except when intolerance to the first agent occurs in the first 3 months of treatment before the assessment of response. As TNF-α inhibitors are the only class of therapies available for AS and nr-ax SpA this decision effectively condemns patients who fail to respond or who lose response to one TNF-α inhibitor to returning to conventional treatment alone (which was not effective in managing their condition). This situation is acknowledged to lead to considerable patient anxiety (Section 4.24) and could disproportionately affect younger patients for the reason that longer disease duration may require more options for treatment.

We disagree with the Appraisal Committee's position on 'switching' for a number of reasons:

1) Second-line and third-line TNF-α inhibitors have been demonstrated to be efficacious in real-world patients

Data from the DANBIO registry (summarised in Section 4.11 of the ACD) demonstrate that sequential treatment with TNF-α inhibitors is efficacious, with small reductions in absolute efficacy with each subsequent line of therapy. The Assessment Group, patient experts, clinical experts, and the Appraisal Committee all acknowledge this finding (Sections 4.12, 4.24, and 4.59). Therefore, it is surprising that the Appraisal Committee feels unable to permit 'switching' in the preliminary recommendation.

One of the reasons given in the ACD relates to the lack of data from randomised clinical trials (RCTs). The NICE Methods Guide does permit the use of non-randomised studies where there is a need to supplement RCT data, with appropriate recognition of the limitations. One such limitation raised by the Assessment Group is that "registries are unreliable because of their selection bias"; however, this is arguably also true for RCTs where enrolled patients are generally fitter than the general population of patients with that condition. In this case we believe it to be beneficial to have data from a real-world population of patients in whom the treatments will be used, as an indicator of likely treatment effects. The existence of patients who have had multiple TNF-α inhibitors within the database also highlights the real clinical need for multiple treatment options in clinical practice.

The cost-effectiveness analysis conducted by one of the manufacturers indicated that ICERs for second-line TNF-α inhibitors are ~£1000 higher than for TNF-α inhibitors used first-line. This should reassure the Appraisal Committee that TNF-α inhibitors used in this way are likely to remain a cost-effective use of NHS resources. We acknowledge that the Assessment Group found there to be some limitations with the sequential modelling; however, we would like to see improvements made to this work and further exploration, rather than it being judged as insufficient to support decision-making.

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2) Limiting patients with AS/nr-ax SpA to one opportunity for biologic treatment is misaligned with other diseases in which biologics are used

In cases of inadequate response to first-line biologic therapy patients with rheumatoid arthritis are able to receive treatment with alternative biologics i.e. rituximab and tocilizumab. Patients with psoriatic arthritis are permitted to receive ustekinumab after "the person has had treatment with 1 or more TNF-alpha inhibitors" (TAG 340). Finally, the switching of biologics is permitted in the management of psoriasis. Given this context, it is not clear whether it is equitable to deny patients with AS and nr-ax SpA the opportunity to find the right biologic therapy from those available to manage their condition.

We note that infliximab has not received a recommendation for AS, and we reiterate our previous comments (submitted in response to the Assessment Group report) around the 'class effect' assumption; we believe that this underestimates the efficacy of Remicade, leading to the judgment that this medicine is not a cost-effective use of NHS resources. Ultimately we believe that patients and clinicians would benefit from access to all efficacious medicines, as part of their armamentarium with which to manage the condition.

Finally, we wish to highlight a statement in the ACD that needs to be amended. In Section 3.3 it states: "Golimumab and infliximab do not currently have a marketing authorisation in the UK for non-radiographic axial spondyloarthritis". Simponi has now received a positive CHMP opinion for nr-ax SpA. Consequently, this statement will be incorrect when final guidance is issued (and potentially when the Final Appraisal Determination is issued, contingent on timelines for EMA approval).

Yours sincerely,

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