AbbVie's response to the Appraisal Consultation Document of ustekinumab for the treatment of active psoriatic arthritis

AbbVie welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) prepared by the Committee for the appraisal of ustekinumab for the treatment of active psoriatic arthritis (PsA).

AbbVie's detailed comments are set out under section headings containing the questions NICE asks consultees to comment on for the ACD consultation.

1. Do you consider that all of the relevant evidence has been taken into account?

AbbVie consider that the majority of relevant evidence has been taken into account by the Appraisal Committee in preparing provisional recommendations detailed in the ACD. However, and as presented in Abbvie's previous response to the first ACD, we emphasize that there are notable data relating to the efficacy of a second-line anti-TNF in a PsA population previously exposed to anti-TNF.

a. Clinical effectiveness of biologic therapy in an anti-TNF exposed PsA population

Abbvie would like to remark the evidence presented in a RCT showing of similar response in both sub-groups anti-TNF therapy in PsA patients with and without prior anti-TNF exposure[1]. Further, results from an observational trial[2], examined the safety and efficacy of adalimumab in patients with active PsA in real-life clinical practices including patients who had been treated unsuccessfully with other anti-TNF agents, showing that patients previously exposed to anti-TNF achieved a good response with adalimumab, albeit numerically lower than biologic-naïve patients. In an open-label extension study[3] show responses to adalimumab in patients with active psoriatic arthritis who have not adequately responded to prior therapy and in another open-label study[4] studied the effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy patients with a prior history of anti-TNF therapy had a high response rate, similar to the population without anti-TNF exposure

Further, The British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) Guideline for the treatment of PsA with biologics look at biologic switching in PsA patients, referencing a body of evidence, and state:

"Multiple open-label studies and registry data have confirmed the potential benefits of switching anti-TNF therapies in patients with PsA. There are no RCTs of sufficient quality to confirm this benefit. Studies of patients with PsA, taken from cohorts and registries of psoriasis and SpA patients, have generally shown a lower response rate to second and subsequent anti-TNF therapies when compared with a first drug, but nevertheless have shown a significant response." [5,6,7,8,9,10,11]

The second sentence relating to RCT data has since been made redundant (see above).

Despite the limitations of not having head-to-head randomised controlled data comparing ustekinumab with anti-TNF therapies in a PsA population and with no formal network meta-analysis of the results presented in this section, AbbVie consider the available evidence suggests that an anti-TNF therapy in an anti-TNF exposed PsA population is likely to be more effective on arthritis symptoms than ustekinumab in the same PsA population.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

AbbVie consider the summaries of clinical and cost-effectiveness from the manufacturer and the ERG to be, on the whole, reasonable interpretations of the evidence. Both manufacturer and ERG addressed several limitations of the economic model and tested it further is sensitivity analyses. However, there are still important limitations in both model structure and parameter. These limitations have been considered by the Appraisal Committee and reflected in the provisional recommendations but AbbVie would like to discuss further the following points in relation to the derivation of cost-effectiveness in the manufacturer's submission:

a. HAQ-DI progression over time in ustekinumab treated patients

The Committee consider in the last ACD that the assumption of a maintained fixed improvement in HAQ-DI over time might not the most appropriate, because of the different mechanism of action of ustekinumab. Further, the Committee's acknowledgment of the differences in radiographic progression presented and the possibility of some worsening of HAQ-DI score during treatment with ustekinumab, leading to a decrease in the cost effectiveness. However, it is noted that the model assumptions were sufficient for the Committee to make a decision.

AbbVie do not consider the data presented to be comparable with radiographic progression data for the licensed anti-TNFs in PsA, and therefore do not consider that the same modelling assumptions are appropriate when evaluating cost-effectiveness. Further, AbbVie do not consider this to be an appropriate assumption for the anti-IL 12/23 ustekinumab based on its different mechanism of action and on the radiographic progression results presented from PSUMMIT 1 and PSUMMIT 2 Randomized Controlled Trials (RCT's).[12]

AbbVie consider it clinically plausible to assume that an increase in radiographic progression score over time in ustekinumab treated PsA patients will be associated with an increase in functional disability and therefore an increase in HAQ-DI score over time. This assumption is based on the studied relationship between HAQ-DI and radiographic progression in patients with rheumatoid arthritis (RA) investigated in several studies[13,14,15].

b. No PASI improvement in conventional management arm

In the first economic model presented it was assumed that patients treated with conventional management do not experience any PASI improvement, i.e. there are no benefits on the skin from conventional management strategies. As PASI response rates are used within the economic model to generate health state utilities and costs in the base case analysis, AbbVie consider this assumption to overestimate the likely incremental benefits of ustekinumab compared to conventional management in PsA patients. RCT data suggest that patients in the conventional care arm can be expected to have a modest improvement in skin clearance which should be taken into consideration within the model.[16] This assumption of zero benefit of conventional management on PASI improvement is contrary to previous modelling of anti TNF therapy in PsA patients which have used the PASI response rates from placebo arms in the available trials.[17]

This assumption was corrected in the economic model, where skin symptoms from conventional therapy were added and PASI scores and response rates for conventional management was taken from the placebo arm of the mixed treatment comparison and SUMMIT 1 and 2 studies. However, the ERG highlighted the differences in PASI score between people assumed to rebound when they stop biological treatment and the average PASI score for people having conventional treatment.

c. Choice of comparator in different sub-groups

AbbVie consider that the appropriate comparator(s) when ustekinumab is evaluated as a biologic option in an anti-TNF exposed PsA population is other licensed and recommended anti-TNF therapies for the treatment of active PsA including adalimumab, etanercept, golimumab and infliximab. When evaluating ustekinumab in an anti-TNF exposed PsA population, AbbVie **do not** consider the incremental comparison versus conventional management to be reflective of clinical practice in the management of PsA patients in the UK based on current NICE Guidance and clinical guidelines in PsA[18]. Recommendations made in NICE TA's 199 and 220 do not preclude the use of more than one anti-TNF in PsA patients and AbbVie consider it would be routine clinical practice to offer eligible PsA patients more than one anti-TNF if appropriate. In addition, The British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) Guideline for the treatment of PsA with biologics make the following recommendations in relation to biologic switching in PsA patients:

"In the case of failure of an anti-TNF treatment either due to inefficacy or adverse events, an alternative anti-TNF therapy should be considered and response to treatment assessed as for the first anti-TNF agent."

The only scenario in which conventional management strategies would be the appropriate comparator(s) in an anti-TNF exposed population is in those patients who have had an inadequate response with anti-TNF therapies **as a class** (i.e. **all four** currently available anti-TNFs). This is likely to represent a very small patient sub-group.

d. Withdrawal rates for ustekinumab patients

The manufacturer's economic model assumes an annual withdrawal rate of 16.5% for ustekinumab patients in both anti-TNF naïve patients and anti-TNF exposed patients. This withdrawal rate has been used in previous anti-TNF appraisals in PsA[19] but is based on withdrawal rates for PsA patients treated with anti-TNF agents.

Given the different mechanism of action of an anti-IL/12 23 such as ustekinumab, AbbVie consider it would be appropriate for the manufacturer to assess the impact on cost-effectiveness of using the actual withdrawal rates observed in ustekinumab patients from PSUMMIT 1 and 2 in a series of one-way sensitivity analyses. Currently, the manufacturer has assessed the impact on the ICER of varying the assumed 16.5% annual withdrawal rate by an arbitrary +/- 25%, which may or may not reflect the range of withdrawal observed in PSUMMIT 1 and 2.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

AbbVie do not agree with the provisional recommendations made by the Appraisal Committee. Based on the evidence provided by the manufacturer, ustekinumab is unlikely to be a cost-effective use of NHS resources when used in the treatment of active PsA patients either as a first-line biologic option or as an option for PsA patients who have previously been exposed to anti-TNF therapy.

AbbVie consider there are relevant and important differences in radiographic progression data between the classes of biologic therapies in PsA which suggest that using similar modelling assumptions over a lifetime horizon may not be appropriate. AbbVie consider that the results from the data presented do not support the link between radiographic progression and quality of life compared with TNF-alpha inhibitors. Further, results show that ustekinumab is less effective than TNF-alpha inhibitors for PASI75, PASI90 and PsARC response. Finally, the diminishing effectiveness of ustekinumab in an anti TNF-alpha treated population supports the conclusion of continuous treatment with TNF-alpha inhibitors might be a better approach for the treatment of PsA.

4. **Are there any equality related issues that may need special consideration?**

AbbVie are not aware of any equality related issues that may need special consideration in the preliminary recommendations.

References

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