Janssen submission on the draft terms of reference of the Post-market review of biological disease modifying anti-rheumatic drugs (bDMARDs) to treat severe chronic plaque psoriasis

Janssen-Cilag Pty Ltd (herein referred to as Janssen) welcomes the public consultation on the draft terms of reference of the post-market review of biological disease modifying anti-rheumatic drugs (herein referred to as biologics) to treat severe chronic plaque psoriasis. Janssen is the sponsor of ustekinumab (Stelara®) and infliximab (Remicade®) which are both listed on the Schedule of Pharmaceutical benefits (PBS) for the treatment of severe chronic plaque psoriasis.

Janssen note that the purpose of the post-market review is to re-assess the cost-effectiveness of the biologics to treat severe chronic plaque psoriasis in the context of the latest available evidence and best clinical practice. The biologics included in the cost-effectiveness review include; ustekinumab, infliximab, adalimumab (Humira®) and etanercept (Enbrel®).

This submission will firstly comment on the process for conducting the post-market review of the biologics to treat severe chronic plaque psoriasis, followed by comments on each of the draft terms of reference.

Process of conducting the post-market review

Janssen acknowledge that this post-market review for biologics used to treat severe chronic plaque psoriasis will follow the process for conducting post-market reviews as outlined in the post-market review framework published on the PBS website. Janssen note that the post-market review framework is not intended to be prescriptive, as reviews will differ in their complexity and focus. Rather, the framework promotes a consistency in approach to conducting post-market reviews whilst providing flexibility to accommodate the different requirements of each review. The structure of more complex reviews may vary from the post-market review framework and that these reviews may take longer than 12 months to complete. In addition, the post-market review framework specifies that sponsors and stakeholders may provide detailed information on the terms of reference for the Review Reference Group to consider as part of the review (PBS post-market reviews Information for stakeholders, 2014).

The public consultation and submission process

Janssen contend that the draft terms of reference for this post-market review, as outlined below address complex and highly technical issues. These draft terms of reference will require accessing clinical and medicine utilisation data from various sources. Rigorous analysis and evaluation of these clinical, medicine utilisation and potentially cost-effectiveness data will also need to be performed. Therefore, the time required to compile a submission that adequately addresses these draft terms of reference will be significant for sponsor companies and may be more in line with developing an application for reimbursement of a new medicine.

Janssen acknowledge that the draft terms of reference were published on 22 April 2016, thereby providing stakeholders with additional time to develop a submission addressing each term of reference. However, as per the post-market review framework, it is anticipated that stakeholders will only be informed of the final PBAC endorsed and Ministerial approved terms of reference at the beginning of the public consultation process. It is difficult for stakeholders to develop submissions that adequately address the final terms of reference on the basis of draft terms of reference that may be subject to change. Additionally and as previously indicated, Janssen anticipates that preparation of a submission for this post-market review will likely take longer than the time between announcement of the review and the anticipated deadline for submissions in the public consultation process based on a six week period.

Consequently, Janssen request flexibility in the timelines for the public consultation process of this post-market review. Specifically, Janssen request that the duration of public consultation on addressing the terms of reference be increased from the standard six weeks to 10 weeks. Janssen believes that these timelines will provide relevant stakeholders, particularly sponsor companies, sufficient time to develop submissions that completely and adequately address the terms of reference. Janssen consider that the prolonged public consultation process will benefit the PBAC and Department of Health as it will enable the PBAC to make a decision referring to the best available evidence on the basis of rigorous health technology assessment methodologies and principles, whilst fully accounting for all stakeholder perspectives.

Evaluation of public stakeholder submissions

The post-market review framework specifies that the Review Reference Group will consider all submissions in full and that they are made available to the PBAC alongside the draft report for consideration. However, it is not clear from the framework how complex submissions presenting clinical, medicine utilisation and cost-effectiveness data are evaluated, incorporated into the Review Reference Group draft report and considered by the PBAC. Therefore, Janssen requests that the Department of Health communicate, with sufficient lead-time, the process for the evaluation and consideration of all stakeholder submissions made to the post-market review. In addition, Janssen request that complex stakeholder submissions are fully evaluated by the Review Reference Group, or a delegated third party. The data provided by sponsors is critical and invaluable to informing the evidence base for the biologics in severe chronic plaque psoriasis. For example, sponsor companies are able to present clinical and cost-effectiveness comparisons based on unpublished data and analyses using individual patient data. These analyses can be tailored to the circumstances of use of the biologics on the PBS. In contrast the Review Reference Group will not have access to these data and will more likely have to rely on published clinical evidence. Rigorous and thoroughly evaluated data provided by sponsors will enable the PBAC to make a

fully informed decision about the effectiveness, cost-effectiveness and utilisation of these medicines in Australian clinical practice as well as any other relevant factors for consideration.

Janssen requests the Department of Health:

- Be flexible in the timelines for the public submission process of this post-market review, and increase the duration of public consultation on addressing the terms of reference from the standard six weeks to 10 weeks.
- Communicate, with sufficient lead-time, the process for the evaluation and consideration of all stakeholder submissions made to the post-market review.
- Ensure that complex stakeholder submissions are fully evaluated by the Review Reference Group, or a delegated third party as rigorous and thoroughly evaluated data provided by sponsors will enable the PBAC to make a fully informed decision based on the best available evidence, as outlined in the purpose of the review.

Comment on the draft Terms of Reference

1. ***Review current clinical guidelines for the treatment of severe chronic plaque psoriasis and compare to the PBS restrictions for use of biologics in this indication*.**

Janssen would appreciate clarity around this term of reference regarding which clinical guidelines will be subject to review. There are no specific Australian clinical guidelines for the treatment of severe chronic plaque psoriasis. Rather there is a treatment goals consensus statement for moderate to severe chronic plaque psoriasis from a number of Australian dermatologists published as Baker 2013. Is this consensus statement considered to be the Australian clinical guidelines for severe chronic plaque psoriasis for the purpose of this review? In addition, Janssen request clarity as to whether international psoriasis management guidelines are within scope of this review.

When addressing this term of reference, consideration must be given to the fact that the decision for clinicians to adopt recommendations made in clinical management guidelines in clinical practice is optional. In contrast, compliance with the PBS restrictions for access to PBS-subsidised biologic therapy is mandatory. In fact, access to the biologics for severe chronic plaque psoriasis is restricted through the use of the rigorous written Authority Required PBS restrictions, which ensure cost-effective use in PBS eligible population. Therefore, if the review identifies differences between clinical management guidelines for plaque psoriasis and the PBS restrictions for biologics used to treat severe chronic plaque psoriasis, this does not mean that there is high likelihood of use of the biologics outside of the PBS restriction.

2. ***Review and evaluate recent clinical evidence on the efficacy and safety of biologics used in the treatment of severe chronic plaque psoriasis and compare to the evidence considered by PBAC in previous sponsor submissions*.**

Effectiveness of the biologics in real world clinical practice as well as the controlled conditions of a clinical trial is critical to understanding the true performance of a drug. Therefore, Janssen consider that this term of reference should specify that all forms of evidence should be included in the review; such as evidence from randomised controlled trials as well as real world observational studies and analyses of medicine utilisation and persistence.

In addition, the complex PBS restrictions and Authority approval process create unique circumstances of use for the biologics in severe chronic plaque psoriasis in Australian clinical practice. Where many studies, both randomised efficacy trials and observational datasets in other jurisdictions follow patients over time without continuation rules, the PBS imposes strict continuation criteria for the biologics in severe chronic plaque psoriasis based on achievement or maintenance of a PASI75 response (75% improvement in the Psoriasis Area and Severity Index [PASI] from baseline) at a particular point in time. Therefore the most relevant considerations of the relative efficacy of the biologics for severe chronic plaque psoriasis on the PBS, and which should be evaluated in this term of reference, are comparisons of:

- The initial PASI75 response rate at a time point that is consistent with the timing for assessment of response stipulated in PBS restriction for the initial treatment period using the TGA approved and PBS subsidised dosing regimen, and
- Maintenance of a PASI75 response in patients who had achieved or maintained a PASI75 in the previous treatment period. This analysis is supported by the PBAC who have previously indicated that the most appropriate analysis in continuing treatment is maintenance of PASI75 response (adalimumab public summary document, July 2008)

Furthermore, Janssen note that there is very limited published evidence reporting maintenance of PASI75 response (especially maintenance of response according to the circumstances of use on the PBS). However, as Janssen have the individual patient data for ustekinumab and infliximab (Remicade®), analyses mirroring the PBS circumstances of use can be presented. Such evidence will not be available to the Review Reference Group without sponsor input. This further highlights the need for rigorous evaluation, review and consideration of sponsor submissions in this post-market review.

Janssen anticipate that this term of reference will require significant resource and time to access, collate, analyse and present the best available evidence on efficacy and safety for the biologics used to treat

severe chronic plaque psoriasis, supporting Janssen's request above for a prolonged public consultation period and rigorous evaluation of stakeholder submissions.

3. ***Review the utilisation of PBS-subsidised biologics for the treatment of severe chronic plaque psoriasis and compare the patient response in practice to those observed in the clinical trial evidence considered by the PBAC. Compare the efficacy in practice among the PBS listed biologics in terms of time on treatment and discontinuations from treatment.***

Janssen consider that the review of medicines utilisation should use multiple data sources to inform continuation on the PBS. Janssen note that the June 2014 Drug Utilisation Sub-Committee (DUSC) review of biologic medicines used to treat severe chronic plaque psoriasis used Authority approval data which by the DUSC admission will overestimate persistence on the PBS as some patients may not fill in their prescriptions. Comparisons of PBS prescription data with Authority approval data highlights discrepancies which generally support the Authority approval method overestimating persistence. Therefore, Janssen request that this term of reference use PBS prescription data either alone or in addition to Authority approvals data to estimate persistence on the PBS.

In addressing this term of reference the Review Reference Group should compare the PBS persistence or continuation rates for each biologic with the clinical trial data matched as closely as possible to the PBS circumstances of use. That is, initial continuation rates (i.e from the initial treatment period to the first continuing treatment period) should be compared with the initial PASI75 response rate from the randomised trials at a time point that is consistent with the timing for assessment of response stipulated in PBS restriction for the initial treatment period using the TGA approved and PBS subsidised dosing regimen. In comparing continuing treatment, the subsequent PBS continuation rates (i.e first to second, second to third continuing treatment periods and so on) should be compared with the maintenance of PASI75 response in patients who had achieved or maintained a PASI75 in the previous treatment period. Therefore, the PBS continuation rates should be compared with efficacy data presented when addressing the second term of reference. Furthermore, Janssen contend that comparisons of PBS continuation rates for the biologics with the intention to treat results from the clinical trials are flawed and not applicable to Australian clinical practice as they do not account for the unique circumstances of use of the biologics for severe chronic plaque psoriasis on the PBS.

As part of this term of reference, Janssen request that should the Review Reference Group find significant differences between the PBS continuation rates and the continuations rates that would have been expected from the clinical trials and observational data, then reasonable and balanced investigation into the potential causes of the differences should be conducted. The management of patients in clinical

practice is different to how patients are managed in clinical trial settings and management practices evolve over time to optimise patient benefit.

4. ***Subject to the findings from terms of reference 1, 2 and 3, review the cost-effectiveness of biologics for severe chronic plaque psoriasis*.**

Janssen would appreciate clarity around this term of reference. In particular, it would be useful if the Department of Health and the PBAC could specify under what circumstances this term of reference will be considered? If it is determined by the Review Reference Group, PBAC or the Department of Health that this term of reference is addressed in the post-market review, Janssen would appreciate that all relevant stakeholders are notified, and either have the duration of the public consultation period extended to allow sponsors to adequately address this term of reference or if timing does not allow, that sponsors be given the opportunity to make an additional submission at a later date addressing this term of reference.

References

Department of Health. Pharmaceutical Benefits Scheme Post-market Reviews. Information for stakeholders, 2014. http://www.pbs.gov.au/reviews/subsidised-medicines-reviews-files/post-market-review-framework-10-2014.pdf, <accessed 10 May 2016>

Department of Health, Humira (adalimumab) public summary document, July 2008, http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-07/pbac-psd-adalimumab-july08, <accessed 10 May 2016>