Amgen Australia: Submission to the Post-Market Review of Ezetimibe

Amgen welcomes the opportunity to provide a submission to the Post-Market Review of Ezetimibe. Amgen is an interested stakeholder as the Sponsor of evolocumab (Repatha®), a new second-line treatment for hypercholesterolaemia, and more generally as an Industry observer to the conduct of post market reviews.

Amgen acknowledges the government's goals in conducting reviews, namely the desire to improve patient safety, PBS viability, the understanding of utilisation and cost-effectiveness and the quality use of medicines. These goals are particularly important in the setting of cardiovascular (CV) disease as it affects over 3.7 million Australians and is the leading cause of death in this country.[1] Build up of low density lipoprotein cholesterol (LDL-C), the so called 'bad cholesterol', causes hardening and narrowing of the arteries (atherosclerosis) that is strongly associated with an increased risk of heart attack and stroke. Consequently, reducing LDL-C, through appropriate use of medicines, plays a major role in the prevention and management of CV disease. Whilst 1st-line statins are the foundation of medical therapy, access to a range of second-line agents is essential as many patients are not reaching their target LDL-C levels.[2] Ezetimibe has an established and important role in clinical practice. Emerging treatments, like the PCSK9 inhibitor class, of which evolocumab is a member, offer the potential for even greater health gains in the management of high CV risk patients.

Comments from Amgen on each of the three Terms of Reference of the ezetimibe review are provided below.

1. *Review current utilisation of Pharmaceutical Benefits Scheme (PBS) - listed Ezetimibe and Ezetimibe combination products. Any review will consider additional data sources that may inform the current utilisation of Ezetimibe.*

The intended use of ezetimibe on the PBS is as a second-line treatment for certain categories of patients at high CV risk. In its most recent review of ezetimibe utilisation, the main question for the DUSC was whether patients are trialling maximum tolerated doses of a statin prior to commencing on the fixed dose combinations products. The DUSC noted that utilisation data alone would not be able to address this question.[3] This first term of reference notes that "additional" data sources may be considered. Amgen believes that if there are further data on which the PBAC based its recommendation to initiate this post-market review, or which is considered during the review, these should be provided to all stakeholders to be able to review and comment.

[1] http://www.aihw.gov.au/cardiovascular-disease/

[2] Robert J Adams, Sarah Appleton, David H Wilson, Anne W Taylor, Catherine Chittleborough, Tiffany Gill and Richard E Ruffin. Cholesterol-lowering therapy and the Australian Pharmaceutical Benefits Scheme: a population study. Aust Health Rev 2009: 33(2): 325–333

[3] http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/ezetimibe-10-2014

2. *Review recent clinical guidelines for the treatment of hypercholesterolaemia and compare this to how ezetimibe is currently used on the PBS.*

The peak guidelines for the treatment of hypercholesterolaemia, applicable to Australian clinical practice and referenced by local clinicians, were summarised in Appendix 1 of the Medicines Australia submission on the draft terms of reference for this review. These guidelines have been in place since 2012/3 and no new Australian guidelines have been introduced in the intervening period. In order to achieve recommended LDL-C goals, the guidelines recognise that some patients may require additional reduction beyond what can be achieved with statins and that some patients are unsuitable for statin treatment or do not tolerate treatment and recommend the use of ezetimibe in these instances. This is consistent with the positioning of ezetimibe on the PBS.

The DUSC has noted that some overseas guidelines, namely those from the American College of Cardiology and the American Heart Association,[4] no longer recommend prescribing additional cholesterol-lowering drugs, such as ezetimibe, to patients who do not reach targets with statins alone, as reduction in heart attack or stroke risk has not been demonstrated. However, both of these organisations have recently revised this position, issuing an expert consensus statement that recommends the use of additional non-statin therapies, including ezetimibe, in high risk patients who cannot achieve a sufficient LDL-C reduction with statin therapy.[5] Australian guidelines continue to recommend treating to LDL-C targets and support a role for second-line therapies.

3. *Collate and evaluate any recent clinical studies of ezetimibe that report on long term patient relevant outcomes, and use this data to review the cost-effectiveness of ezetimibe.*

If, under terms of reference 1 and 2, utilisation of ezetimibe is found to be consistent with the intent of the PBS listing and recommendations within local clinical guidelines, it is Amgen's view that it is unnecessary to review the cost-effectiveness of ezetimibe. The IMPROVE-IT trial, which reported on long-term patient relevant outcomes with ezetimibe, has shown that the benefit afforded by the simvastatin‑ezetimibe combination in that trial was consistent with that seen in previous statin trials, with a similar reduction in cardiovascular events according to the degree of LDL-C lowering.[6] There have been no other changes in the intervening period in terms of PBS listings, local treatment guidelines or choice of comparator that would warrant reconsideration of the cost-effectiveness of ezetimibe.

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[4] Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2013; Published online before print November 12, 2013, doi: 10.1161/01.cir.0000437738.63853.7a.

[5] Lloyd-Jones DM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol*. 2016; Published online before print in April 2016 doi:10.1016/j.jacc.2016.03.519 2016.

[6] Cannon et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372:2387-2397.

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CV outcomes trials like IMPROVE-IT are expensive to conduct as large patient numbers and lengthy follow-up are required. It is not feasible for Sponsor companies to invest in trials to assess CV outcomes in all patient types in which a lipid lowering therapy is used. By default there will be a wider body of LDL-C outcome evidence across diverse populations. LDL-C reduction has always been considered a valid surrogate outcome by regulatory and reimbursement agencies and the evidence supporting this has strengthened over time. The patient relevant outcomes demonstrated in a CV outcomes trial, in conjunction with LDL-C outcome evidence, should be considered sufficient to support reimbursement of a product across a range of populations of interest.

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Amgen looks forward to reviewing the outputs of the ezetimibe review and being involved to the extent possible as the review progresses. We advocate continued adherence to the framework for post market reviews agreed between Medicines Australia and the Department of Health. Given the complexity of the review, the established role of ezetimibe, potential impact to important new treatments and the vast range of stakeholders impacted, Amgen recommends holding a stakeholder forum during the review to ensure all views are appropriately considered with an aim to optimise the management of CV disease in Australia.