CATAG
Council of Australian Therapeutic Advisory Groups

CATAG submission:

Public Consultation on the Post-market Review of Ezetimibe

April 2016

The Council of Australian Therapeutic Advisory Groups (CATAG) is an authoritative, expert, consensus-based collaboration of representatives from all Australian State and Territory Therapeutic Advisory Groups or their jurisdictional committee equivalents.

CATAG aims to standardise and improve medicines use primarily (but not exclusively) in the hospital sector across Australia through information sharing, advice and advocacy activities.

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1. Summary of CATAG findings

CATAG's submission to the PBS Review aims to provide insight into the hospital-based prescription and utilisation of ezetimibe and the influence that hospital-based prescription of ezetimibe may have on community prescribing practices of ezetimibe. All Australian states and territories contributed to the information in this submission and formulary listings for state-wide health services, healthcare networks and individual hospitals were provided. Jurisdictions were also requested to provide information regarding the incorporation of ezetimibe into clinical guidelines or policies for use in the hospital setting.

Responses were received from all jurisdictions. In summary, the majority of formularies of all jurisdictions (whether state-based or hospital/district-based) listed ezetimibe according to the PBS criteria. The majority of states and territories do not list the combination products of ezetimibe and statin (simvastatin or atorvastatin) on their formularies for initiation or continuation of treatment.

There were minimal local guidelines or protocols referring to or recommending ezetimibe use in hospital inpatients. The Therapeutics Guidelines: Cardiovascular and Cardiac Society of Australia and New Zealand/Heart Foundation guidance documents are the most relevant and most likely to influence hospital-based prescribers of ezetimibe.

Prescription of ezetimibe within hospitals is influenced by the PBS criteria, as most formulary listings state the same criteria. There is minimal initiation of treatment in hospital and, when it does occur, it is usually concordant with the PBS restrictions. The prescription of ezetimibe within hospitals is heavily influenced by community-based prescribing, indicated by the feedback from hospitals and the lack of ezetimibe-related policies and protocols within hospitals.

2. Background

2.1 Ezetimibe TGA registration and PBS listing

The TGA indications for ezetimibe are primary hypercholesterolaemia (heterozygous familial and non- familial) with or without a statin as adjunctive therapy to diet; homozygous familial hypercholesterolaemia with a statin; and, reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.

The PBS subsidises the same general indications as the TGA, however there are additional clinical criteria, which restrict ezetimibe prescription under the PBS. Ezetimibe must be used in conjunction with diet and exercise, be co-administered with a statin, the patient's cholesterol levels must be inadequately controlled with a statin and the patient must belong to a high risk cardiovascular population (with conditions such as coronary heart disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus and a family history of early coronary heart disease or pre-existing hypertension) or must be statin-intolerant or have contraindications to statin treatment.

2.2 Recent evidence regarding ezetimibe use

The most recent randomized-controlled trial IMPROVE-IT investigating ezetimibe 10mg and simvastatin 40mg vs simvastatin 40mg use in patients hospitalized for an acute coronary syndrome within the preceding 10 days and elevated LDL cholesterol levels. This study found there was a modest benefit when ezetimibe was used in combination with a statin over a six year period with a statistically significant reduction in the primary composite endpoint of cardiovascular death, major coronary event or nonfatal stroke (HR 0.95, CI 0.89-0.99). Hospitals did not report that the IMPROVE-IT study had had any significant impact on ezetimibe prescription. The magnitude of the results was in accordance with other studies investigating the association between LDL-cholesterol reduction and future cardiovascular events. It is currently unclear what effect the results of the IMPROVE-IT study have had on Australian community-based clinical practice. The current PBS criteria for subsidised ezetimibe prescription predate the publication of the IMPROVE-IT study.

CATAG notes that the National Institute for Health and Care Excellence (NICE) in the United Kingdom recently updated their guidance on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia.[1] This guidance considered the findings of the IMPROVE-IT trial in their analysis of clinical effectiveness but not cost-effectiveness. NICE concluded the clinical effectiveness of ezetimibe using the updated evidence base (chiefly, the results of the IMPROVE-IT study) was consistent with the previous NICE technology appraisal guidance on ezetimibe.

The summarised recommendations from the NICE guidance remain:

I. Ezetimibe mono-therapy is recommended as a treatment option for hypercholesterolaemia, when statin therapy is contraindicated or intolerable and
II. Ezetimibe in combination with a statin is a recommended treatment for hypercholesterolaemia in patients who have started statin therapy, when LDL is not adequately controlled.

On review the current TGA ezetimibe listing for primary hypercholesterolaemia does not differ significantly from the NICE guidance. It does not restrict use to the same degree as the PBS clinical criteria, but does recommend that the NICE ezetimibe guidance be used in conjunction with NICE's guidelines on Cardiovascular disease: risk assessment and reduction, including lipid modification[2] and Familial hypercholesterolaemia: identification and management[3].

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[1] National Institute for Health and Care Excellence*; Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia* February 2016. nice.org.uk/guidance/ta385.

[2] *Cardiovascular disease: risk assessment and reduction, including lipid modification* July 2014. https://www.nice.org.uk/guidance/cg181

[3] *Familial hypercholesterolaemia: identification and management* August 2008. https://www.nice.org.uk/guidance/cg71

3. CATAG Member Survey

CATAG surveyed its members in order to provide insight into hospital-based utilisation of ezetimibe and the influence that hospital-based prescription of ezetimibe may have on community prescribing practices or vice versa

Accordingly, CATAG members were asked to provide information on the following:

I. Formulary[4] listings for ezetimibe as a single entity or in combination products within each jurisdiction; and, whether these listings were hospital, local health network or statewide formulary listings.

II. Clinical guidelines or policies that refer to ezetimibe within the jurisdiction.

4. Survey Results

4.1 Formulary listings

In general, the formularies of all jurisdictions (whether state-based or hospital/district-based) listed ezetimibe as per the PBS criteria discussed above. No additional criteria or restrictions were required for hospital prescribers to initiate ezetimibe treatment other than the PBS criteria.

Exceptions included:

I. The Queensland State-wide Formulary: The listing restricts prescription to "Specialist Staff use as per the PBS indications". In addition, Indigenous Health Workers (under their Queensland Health (Drugs and Poisons) Regulations, Drug Therapy Protocol), nurse practitioners and doctors can prescribe ezetimibe for chronic kidney disease and chronic heart disease as per the Primary Clinical Care Manual (2013), which guides those working in rural and remote health service settings.

II. NSW: Of the 13 respondent hospitals/LHDs, one hospital and one LHD listed ezetimibe on their formularies according to the more general TGA criteria. It is not known whether this leads to patients being prescribed ezetimibe who do not meet the PBS criteria. Three hospitals/LHDs did not list ezetimibe on formulary but provided it to patients as part of ongoing therapy when patients were prescribed the medicine prior to admission.

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[4]A continually updated list of medications and related information, representing the clinical judgment of physicians, pharmacists, and other experts in the diagnosis, prophylaxis, or treatment of disease and promotion of health. A formulary includes, but is not limited to, a list of medicines and medicine-associated products or devices, medication-use policies, important ancillary drug information, decision-support tools, and organisational guidelines. American Society of Health-System Pharmacists. ASHP guidelines on the pharmacy and therapeutics committee and the formulary system. Am J Health Syst Pharm. 2008;65:166-75.

The majority (75%) of states and territories do not list the combination products of ezetimibe + statin (simvastatin or atorvastatin) on their formularies for initiation of treatment. This means when a patient is initiated on ezetimibe treatment whether they are on a statin or not, they will be initiated on the single entity product. On discharge from hospital it would be expected the patient would continue on treatment using single entity products until reviewed by a general practitioner in the community.

The majority (63%) of states and territories do not list the combination products of ezetimibe + statin (simvastatin or atorvastatin) on their formularies for continuation of treatment. On discharge from hospital it would be expected the patient return to using the combination product they were using prior to admission, unless their treatment had been altered as a result of their hospitalisation.

Table 1 provides more detailed information regarding ezetimibe and combination product formulary listings according to jurisdiction.

4.2 Clinical guidelines or policies

The majority of jurisdictions reported no state-wide, LHD or hospital-based clinical guidelines or protocols referring to ezetimibe. The most relevant national guidelines for hospital-based prescribers would be the *Therapeutic Guidelines: Cardiovascular* and the Cardiac Society of Australia and New Zealand *Guidelines for the Diagnosis and Management of Familial Hypercholesterolaemia*.

[redacted] is the only reported hospital to have a protocol referring to ezetimibe and this was for ambulatory patients attending an outpatient clinic: "Treatment protocol, ezetimibe and fenofibrate in the lipid disorders clinic"

4.3 Further commentary

Jurisdictions reported that initiation of ezetimibe in hospital was infrequent. Reasons for this included:

a) management of hypercholesterolaemia with ezetimibe is not an 'acute treatment';
b) that prescription of more potent statins or statin dose adjustment is more likely to be addressed before ezetimibe is prescribed when cholesterol management was judged inadequate; and,
c) there are no local protocols recommending ezetimibe use in hospital inpatients.

A number of respondents commented that the use of ezetimibe within hospitals is primarily influenced by community-based prescribing.