ABSTRACT

OBJECTIVES: When there are no direct head-to-head trials versus an appropriate comparator, indirect comparisons are commonly performed to support a clinical claim and relative pricing. In Australia, Public Summary Documents (PSDs) reporting on the Pharmaceutical Benefits Advisory Committee’s (PBAC) decision-making process relating to government reimbursement of medicines, have been published since July 2005. A review of PSDs specific to drugs where the primary claim was based on indirect evidence was undertaken to assess the success of the approach and identify the PBAC’s main concerns relating to the methodology.

METHODS: All PSDs published between July 2005 and November 2012 where the primary evidence was based on an indirect comparison, either as simple or a mixed treatment comparison, were reviewed. Data relating to comparator, clinical claim, economic analysis, and PBAC concerns were extracted and analysed.

RESULTS: PSDs relating to 105 products using an indirect comparison as the primary analysis were reviewed. A total of 70 (67%) submissions were recommended; the remaining submissions were rejected (32, 30%) or deferred (3, 3%). Of those claiming non-inferiority, 60 (71%) submissions were recommended by the PBAC. Of those claiming superiority, the PBAC accepted the clinical claim for 10 (44%) submissions; 9 (29%) received a price premium. The PBAC expressed concerns relating to the indirect comparisons in 56 (53%) PSDs. The key issues related to the exchangeability of the trials as a consequence of different patient populations (25%), quality of trials (24%), and dosing (18%).

CONCLUSIONS: Clinical comparisons based on indirect evidence are associated with increased uncertainty related to the exchangeability of the trials. The PBAC usually accepts evidence to support a claim of non-inferiority, but rarely the same in regard to superiority.

INTRODUCTION

In Australia, submissions for drugs are lodged by sponsors and the Pharmaceutical Benefits Advisory Committee (PBAC) makes recommendations to the Minister for Health on their listing on the national Pharmaceutical Benefits Schedule (PBS). Information on the outcomes of submissions to the PBAC is made public on the Department of Health and Ageing website, and further detail is provided in Public Summary Documents (PSDs). The PBAC guidelines state that direct evidence from randomised controlled trials (RCTs) to support a non-inferiority or superiority claim is preferred. The PBAC guideline recognises that indirect evidence can be an acceptable alternative where direct evidence is not available.1,2

OBJECTIVES

• The purpose of this study was to review the outcomes of Australian submissions that have used an indirect comparison as the primary evidence to support the clinical and economic claim.

• To document the reasons for rejection or deferral of applications, and methodological approaches and examine the impact these had on the final recommendation.

METHODS

A database of 590 PSDs published between July 2005 to November 2012 was searched for the term “indirect comparison”.

All PSDs identified in the search were reviewed and excluded if:

• the indirect comparison was supportive or secondary to direct head to head trial data,

• the comparison was made using data from single-arm trials. These products were mainly confined to oncology and tended to have different methodological approaches.

If there were multiple submissions for the one product, these were treated as separate submissions unless there had been a clear change in the approach taken.

Once the dataset was confirmed, all PSDs for the drug, indication, and outcomes were reviewed noting the final recommendation, the comparator used as part of the indirect comparison, the clinical and economic claim, and any points of concern or uncertainty relating to the indirect comparison.

RESULTS

Dataset

Of the 590 PSDs published between July 2005 to November 2012, 105 PSDs were identified from the initial “indirect comparison” search.

After applying the exclusion criteria, the dataset comprised 122 submitters. Some of these PSDs were identified for the same indication and were therefore counted as one submission in the 105 individual product submissions.

Outcomes

Of the 105 individual product submissions, 70 (67%) were recommended; 32 (30%) rejected and 3 (3%) deferred (Figure 1).

When the outcomes were examined by year, it appears that success rates were higher before 2009, the rejection rate increased after 2008, the year of the release of the ICWG report.

Clinical Claim

Non-inferiority

The clinical claim was non-inferiority in 84 (86%) submissions. Of those claiming non-inferiority, 60 (71%) submissions were recommended by the PBAC.

Superiority

The clinical claim was superiority in 21 (20%) of submissions. The PBAC accepted the clinical claim to some extent in 10 (48%) of cases.

Despite recognition of a clinical advantage, the PBAC ultimately rejected the submission in 11 cases. The main reasons for rejection were the unacceptability of the evidence (10 cases), the methodological approach not being acceptable to the PBAC, or a combination of both.

In the four submissions where PBAC accepted the superiority claim at some extent, two were recommended on a cost minimisation basis due to uncertainty with the overall clinical evidence and two were recommended on an uncompensated high IER and uncertainty in relation to the clinical claim.

Points of Concern

The 34 submissions that were initially rejected, a variety of issues were raised, such as the wrong choice of comparator, high or uncertain IERs, and overall concern relating to the clinical claim and supporting evidence. Concerns regarding the appropriateness of the indirect comparisons appeared to be an important issue for 9 (26%) PSI submissions.

The most commonly reported issues irrespective of the final recommendation were:

• differences in the patient population (25%). These differences were either due to different selection criteria and/or patient demographics.

• differences in the quality and method of trials (24%). These related to differences in the definition or timing of outcome measures or differences in follow up.

• differences in circumstances of use (18%). These issues were primarily around dosing and the use of concomitant medications.

CONCLUSIONS

• Indirect comparisons are often considered to be associated with increased uncertainty related to the exchangeability of the trials. Nevertheless, overall a high proportion of those identified in this research resulted in a positive recommendation.

• In recent years there appears to be an increase in the number of rejections; however, this is not necessarily due to indirect evidence.

• The PBAC is more likely to accept indirect evidence to support a claim of non-inferiority than superiority.

REFERENCES
