Rifampicin for MRSA

While reviewing an article on bacteria with resistance to multiple antibiotics (Aust Prescr 2010;33:68–71), the Editorial Executive Committee found an anomaly in the availability of rifampicin on the Pharmaceutical Benefits Scheme (PBS). The restrictions for rifampicin do not include the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). For infections which can be managed with oral antibiotics, rifampicin is often given with fusidic acid. The PBS restrictions for fusidic acid require it to be used with another antibiotic in the treatment of proven serious staphylococcal infections. The other antibiotic is likely to be rifampicin, but this cannot be prescribed as a pharmaceutical benefit.

The purpose of using two antibiotics is to try to prevent further resistance. The Editorial Executive Committee therefore asked for the advice of the Pharmaceutical Benefits Advisory Committee on how to resolve the apparent anomaly in the PBS restrictions.

PBAC response:

The PBAC has to consider the terms of marketing approval of a product. This approval is granted by the Therapeutic Goods Administration (TGA) and specifies the conditions in which the drug has shown acceptable safety and efficacy. The PBAC is not in a position to recommend that a drug be listed outside the terms of marketing approval specified by the TGA.

Currently, rifampicin is approved by the TGA for the treatment of tuberculosis, leprosy, prophylaxis of meningococcal disease and prophylaxis of household contacts of patients with *Haemophilus influenzae* type B. Under the *National Health Act 1953* there is no provision for the subsidised supply of an item listed as a restricted benefit for use in a condition which lies outside the terms of the restriction specified in the Schedule of Pharmaceutical Benefits. The current PBS listing for rifampicin reflects the TGA registration and so rifampicin cannot be prescribed for MRSA under the PBS.

The PBAC is concerned that rifampicin is not available as a pharmaceutical benefit for treating MRSA and has previously asked the drug's sponsor to seek marketing approval for this indication. However, neither the PBAC nor the government can compel a manufacturer to apply for registration of a drug for a particular indication.

Industry response:

The Editorial Executive Committee sought responses from the manufacturers of rifampicin in Australia.

Dr Alex Condoleon, Medical Director Australia & New Zealand, Sanofi-aventis, comments:

The availability of rifampicin as a pharmaceutical benefit in combination with fusidic acid for methicillin-resistant *Staphylococcus aureus* (MRSA) would require supporting evidence to achieve registration with the TGA and subsequently reimbursement through the PBS. Sanofi-aventis has therefore searched the literature about this combination, to determine the feasability of increasing access to this regimen for patients.

Treatment guidelines

The Therapeutic Guidelines: Antibiotic[1] lists the combination of rifampicin and fusidic acid as a treatment option for recurrent staphylococcal skin infections (including MRSA-positive infections), and MRSA osteomyelitis involving the bone or joint prostheses, in both adult and paediatric patients. Similarly, the Australian Medicines Handbook[2] lists combination treatment of MRSA infection as an indication under both the monographs for rifampicin and fusidic acid.

Contrary to the Australian guidelines, the combination is not included in DrugDex Evaluations,[3] the American Hospital Formulary Service (AHFS) Drug Information,[4] the Centers for Disease Control and Prevention (CDC),[5] the World Health Organization (WHO),[6] and the European Centre for Disease Prevention and Control.[7]

Published clinical studies and reviews

A search of the medical literature retrieved a small number of studies evaluating the combination for the management of MRSA infections and a large number of review articles on the management of MRSA infections. This search is subject to the limitations inherent in these databases and cannot be considered exhaustive.

Studies in adults

Two small (n=<12) Australian trials[8,9] studied the combination of rifampicin and fusidic acid for the treatment of MRSA infections in orthopaedic patients and patients with cystic fibrosis respectively. Both studies found this combination to be effective at eradicating MRSA infection.

Studies in children

None of the small number of studies[10–13] of MRSA infections evaluated the combination of rifampicin and fusidic acid.

Review articles

Two of four review articles[14–17] on the management of MRSA infections specifically listed the combination of rifampicin and fusidic acid as a treatment option for MRSA infections.[16,17]

None of six paediatric review articles[18–23] specifically listed the

combination of rifampicin and fusidic acid as a recommended treatment option. However, five of these reviews[18–22] listed rifampicin as a treatment option, stating that it must be used in combination with other antibiotics.

Conclusion

Upon current assessment of available data there appear to be inconsistencies in treatment guidelines and only a small number of studies evaluating the combination of rifampicin and fusidic acid for the treatment of MRSA infections. Sanofi-aventis therefore does not believe that the evidence base exists to satisfy regulatory requirements to support this additional indication. However, we are open to reassessing options should further evidence emerge, or be brought to our attention, that could support a formal regulatory submission.

Note: References are available online with this article in Vol. 33 No. 5 at www.australianprescriber.com.

Dr Greg Pearce, Director, Medical Affairs, Alphapharm, comments:

Most parties with an interest in making older medicines more freely available, at an affordable cost, for unapproved indications agree that this is an important issue. Unfortunately, no-one has been able to devise a satisfactory process for registering the indication and listing the product on the PBS. At a minimum, this process needs to balance evidence requirements, commercial considerations and regulatory scrutiny to a point where the documentation expectations are consistent with the commercial objectives of a potential supplier.

This impasse remains, despite meetings between the Royal Australasian College of Physicians, the TGA and industry representatives, a consultancy commissioned by the Department of Health and Ageing on behalf of the Paediatric Medicines Advisory Group, and direct representation by Alphapharm to the TGA.

Alphapharm is sympathetic to addressing this gap in our ability to deliver quality use of medicines but cannot move forward under the current regulatory and reimbursement framework. Recent PBS reforms have shifted the sponsor's fulcrum even further away for supporting these requests.

The company would support any further discussions aimed at developing innovative approaches to improve access to treatment. These would need to match the costs and evidence requirements for registration against the needs of a manufacturer to achieve a financial return which at least covers the resource and financial costs associated with applying for approval of a new indication.

In memoriam

Maureen Ryan Editorial Assistant *Australian Prescriber* 2003–10

The Editorial Executive Committee and staff of *Australian Prescriber* are deeply saddened by the sudden death of Maureen Ryan. Maureen was an essential member of the small team which produces *Australian Prescriber*, having worked as the Editorial Assistant for almost seven years.

The Editorial Assistant has a variety of duties and Maureen's many talents and diverse career path suited the role. Maureen had previously been the Business Manager of the Canterbury Division of General Practice. She was therefore able to implement some new procedures to enhance the efficiency of the journal's editorial processes. These procedures streamlined communications with authors, referees and pharmaceutical companies. Maureen also improved the formatting of the articles and became an expert in deciphering the Editor's handwriting.

An important part of Maureen's work was acting as the Secretary of the Editorial Executive Committee. She organised meetings efficiently ensuring that the large agendas were always prepared on time and that the minutes of the meetings were accurately recorded.

Maureen was a very patient person. This attribute was of great assistance when pursuing contributors who had missed their deadlines.

In July Maureen won an EPIC award from the NPS. This reflected her excellence, passion, integrity and commitment. Maureen truly believed that supporting health professionals with independent information would improve people's health through the quality use of medicines. She made a great contribution to *Australian Prescriber* and the NPS and will be sorely missed.