Australian Government
Department of Health
Therapeutic Goods Administration

Interim guideline on microbial resistance risk data for antibacterial medicinal products

Guideline to assist sponsors provide information for CTD Module 1

Version 1.0, September 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Medicines Authorisation	XX/09/2014

Contents

Introduction

Sponsors of antibacterial medicinal products for human use in Australia are required to provide data to address recommendations in the Report of the *Joint Expert Advisory Committee on Antibiotic Resistance* (1999)[1] and the *Commonwealth Government Response to the Report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance* (2000)[2], the JETACR Report.

The data that should be included with applications to register a new antibacterial medicinal product or to extend use of products already registered in Australia are:

- microbial resistance safety data, including data on the propensity for promoting resistance and cross-resistance, as a basic requirement for the assessment of all new antibacterial agents, and
- Australian human antibiotic-resistance prevalence data in the Product Information.

This Guideline applies to systemically and topically administered antibacterial medicinal products as well as to composite packs and combination products that contain antibacterial agents.

The *Risk assessment of microbial resistance* document submitted by the sponsor will be reviewed by TGA and advice from the Advisory Committee on Prescription Medicines (ACPM) will be sought for application to register a new antibacterial medicinal product or if rejection is proposed for an application to extend the use (e.g. new indication, new population, changed dosage regimen or new dosage form) of a registered antibacterial medicinal product.

Risk assessment of microbial resistance

The *Risk assessment of microbial resistance* is expected to be qualitative in part, although quantitative data should be provided where possible.

A copy of the *Risk assessment of microbial resistance* document should be included in CTD Module 1 of the dossier.

Although review will be facilitated by provision of a separate risk assessment document it is acceptable to cross-refer to other submitted documentation to describe specific data within the risk assessment.

Data requirements

The *Risk assessment of microbial resistance* document should include the following information:

Background information

- Name and identification of the antibacterial agent and medicinal product

[1] Commonwealth Department of Health and Aged Care and the Commonwealth Department of Agriculture, Fisheries and Forestry -Australia. The Use of Antibiotics in Food-Producing Animals: Antibiotic-Resistant Bacteria in Animals and Humans. Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR). September 1999. <http://www.health.gov.au/internet/main/publishing.nsf/Content/A7CAB5EED5E82D38CA257BF0001B098A/$File/jetacar.pdf>

[2] Commonwealth Department of Health and Aged Care and the Commonwealth Department of Agriculture, Fisheries and Forestry-Australia. The Commonwealth Government Response to the Report of the Joint Expert technical Advisory Committee on Antibiotic Resistance (JETACAR) August 2000 <http://www.health.gov.au/internet/main/publishing.nsf/Content/7B83F0073DE3FC10CA257BF0001D4D0D/$File/CWealth%20Govt%20Response%20to%20JETACAR.pdf>

- Chemical name (AAN)
- Trade name
- Manufacturer's code number and/or synonyms
- CAS Registry number
- Chemical structure
- Quantitative composition (active)
- Pharmaceutical dose form
- Route of administration
- Indications (currently approved/proposed)
- Dosage (currently approved/proposed)
- Pack sizes

· Class of antibacterial agent

- Chemical relationship to other members of class and related classes
- Mode of action of the antibacterial agent
- Mechanisms of resistance
- Registration status of the class in humans in Australia
- Registration status of the class in animals in Australia

Risk assessment

Hazard characterisation

The hazard for development of resistant microorganisms or transferable/transposable resistance genes associated with the antibacterial medicinal product in the use proposed may be characterised by providing information on resistance and genetics of resistance.

Bacterial resistance

· The hazard with regard to details of bacterial resistance patterns in relevant microorganisms *in vitro* may be characterised by providing:

- Minimum inhibitory concentration (MIC) data of the antibacterial agent against bacterial species likely to be affected. MIC distribution data should be presented for targeted bacterial species and for relevant non-targeted bacterial species. Estimated rates of development of the expression of resistance, such as indicated from *in vitro* studies of passaged microorganisms in the presence of the antibacterial agent, may be included.
- Details of microbial resistance patterns in relevant human isolates which have emerged with the use of the antibacterial agent, or related substances, overseas and/or in Australia should be provided when available. This would include changes identified in MICs of the antibacterial agent against isolates of bacterial species likely to be affected collected from clinical trials or from wider clinical use. The risk assessment should state whether Australian data are included and Australian data should be provided where available and recent.

- Data on mechanisms of resistance pathways in relevant microorganisms.
- Data on *in vitro* cross-resistance with other antibacterial agents in the same class in targeted and non-targeted bacterial species.
- Data on co-selection of resistance by unrelated antibacterial agents

Genetics of resistance

- The genetics of resistance may be characterised by providing:
  - Data on resistance genes.
  - Location of resistance genes (chromosomal, transferable elements).
  - Data on transfer of resistance genes between bacterial species.

Exposure characterisation

The probability of exposure to the hazard estimated for specified exposure conditions may be estimated by providing:

- Projected quantities of use.
- Projected pattern (e.g. community and/or institutional use; oral and/or injectable dosage forms) and extent of use.
- Comment on dose response and dosage regimens. This could include an assessment of whether pharmacokinetic/pharmacodynamic relationships are optimised to minimise selection for resistance without compromising treatment outcome (see CPMP/EWP/2655/99 *Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal product* and CPMP/EWP/558/95 rev 2 *Note for Guidance on Medicinal Products for Treatment of Bacterial Infections*).
- Evidence concerning the potential for resistant microorganisms or resistance transferable genetic elements to spread through the community.
- Description of any proposed strategies or recommendations to promote prudent use of the product.
- Assessment (in terms of the probability categories[3] 'negligible', 'low', 'medium', 'high' and 'not assessable') of the probability of exposure to resistant microorganisms or resistance transferable genetic elements when the product is used as proposed.

Impact characterisation

The potential impact of development of resistance to the antibacterial agent may be characterised by providing:

- Assessment of the potential consequences of the development of resistant microorganisms or resistant plasmids in human infections.
- The rank-order for the antibacterial medicinal product with regard to the perceived or known clinical importance of the class of antibiotics in human medicine, based on *Antimicrobial Resistance Standing Committee* (AMRSC) Importance Ratings categories[4]:

[3] The probability categories in this context are defined as follows: 'negligible': probability is extremely low or negligible; 'low': probability is low but clearly possible; 'medium': probability is likely; 'high': probability is very likely or certain)

  - High: These are essential antibiotics for treatment of human infections where there are few or no alternatives for many infections. Also have been called "critical", "last-resort" or "last-line" antibiotics.
  - Medium: There are other alternatives available but less than for those classified as Low.
  - Low: There are a reasonable number of alternative agents in different classes are available to treat most infections even if antibiotic resistance develops.

- Comment on the impact of failure of antibacterial treatment, in the proposed indications and in other indications.
- Comment on the benefits of the antibacterial medicinal product in human health.
- Assessment of the impact of disease caused by infections due to antibiotic resistant microorganisms (and transferable genetic elements) in humans in the risk categories of negligible, low, medium, high or not assessable. Impact should be considered on the levels of both the treated patient and the community.

Risk characterisation

An assessment of the uncertainty of data used to characterise the risks[5] associated with development of resistance to the antibacterial agent should be provided.

The risk characterisation assessment findings may be summarised in tabular form as shown below. Hazard is not categorised. Place a tick in the column that characterises the exposure and the impact. For example, if the exposure is low and the impact is negligible, a tick is placed in the 'low' column for exposure and in the 'negligible' column for impact.

Risk category[6]					
	Negligible	Low	Medium	High	Not assessable
Exposure					
Impact					

A separate risk summary may be necessary for each proposed indication, dosage regimen and route of administration.

The conclusions and recommendations of the risk characterisation in support of the proposed use pattern should include proposals for minimisation of potential for development of microbial resistance and justification of risk/benefit balance of use of the antibacterial medicinal product in human health in the Australian population.

[4] Antimicrobial Resistance Standing Committee. AMRSC Importance Ratings and Summary of Antibacterial Uses in Humans in Australia. July 2014.
[5] Australian/New Zealand Standard Risk Management AS/NZS 4360: 2004
[6] The probability (risk) categories in this context are defined as follows: 'negligible': probability is extremely low or negligible; 'low': probability is low but clearly possible; 'medium': probability is likely; 'high': probability is very likely or certain)

Microbial resistance: Pharmacovigilance

Risk Management Plan

The Risk Management Plan (RMP) should include "resistance" as an ongoing safety concern and include a cross-reference to the relevant part of Module 1.

The RMP should include details of any proposed 'Additional risk minimisation activities' such as education of prescribers and the community.

Post-marketing requirements

Sponsors should note the recommendations in the JETACAR report[1] for inclusion of Australian human antibiotic-resistance prevalence data in the Product Information (under *Pharmacology*) and the updating of such information. After registration sponsors should monitor information on the prevalence of resistance in Australia (eg. from independent surveys, cooperative studies, literature reports, company data and other sources including any future national system of surveillance for antibiotic resistance) and provide such information to the TGA initially in Periodic Safety Update Reports (PSURs) and subsequently in applications to update the Product Information when appropriate.

Note that some approvals for registration may require, as a condition of registration, sponsors to implement on-going monitoring of resistance at a nominated number of Australian sites.

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Reference/Publication #