Australian Government
Department of Health
Therapeutic Goods Administration

Antibiotic resistance guidance

Assessment of risk of resistance development pre- and post-market

Version 2.0, March 2017

TGA Health Safety Regulation

Contents

This guidance is to assist sponsors of antibacterial prescription medicines (antibiotics) collect and provide appropriate information about the development of antibiotic resistance pre- and post-market. Please note that we require **Australian** human antibiotic-resistance prevalence data.

Antibiotic resistance data requirements

Sponsors making applications for antibacterial medicines for human use in Australia are required to provide data to address recommendations in both:

- The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans: 1999 report by the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR), jointly established by the then Minister for Health and Aged Care and the then Minister for Agriculture, Fisheries and Forestry
- The Commonwealth Government Response to the report of JETACAR August 2000 (available from the National Library of Australia)

When to include antibiotic resistance data

This guidance applies to all prescription antibacterial medicines:

- topical and systemic antibacterial medicines
- combination medicines containing antibacterial medicines
- composite packs containing one or more antibacterial medicines.

Use this guidance when you apply to:

- register a new antibacterial medicine
- extend the use of a registered antibacterial prescription medicine, e.g.:
  - new indication
  - new population
  - changed dosage regimen
  - new dosage form
- change the Product Information to include updated antibiotic resistance data

Reviewing the data

We review the *Risk assessment of the development of antibiotic* resistance provided by the sponsor and make an assessment of the risks.

We seek advice from the Advisory Committee on Medicines (ACM) about the risks of the development of antibiotic resistance:

- for all new antibacterial registration applications
- when we propose to reject an application to extend the use of a registered antibacterial medicine

Risk assessment of the development of antibiotic resistance

Include the *Risk assessment of the development of antibiotic resistance* in Module 1.12.

The *Risk assessment of the development of antibiotic resistance* is expected to be qualitative in part, but please provide quantitative data where possible. The entire risk assessment should be located in Module 1.12, but the data may be located in Module 4 or 5, if this is appropriate.

In the *Risk assessment of the development of antibiotic resistance* include:

- Background information
- Hazard characterisation
- Exposure characterisation
- Impact characterisation
- Risk characterisation

Background Information

Name and identification of the antibacterial agent and medicine

- 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

Hazard characterisation

The hazard for development of resistant bacteria or transferable/transposable resistance genes associated with the antibacterial medicine in the use proposed may be characterised by providing information on:

- Bacterial resistance
- Genetics of resistance

Bacterial resistance

The hazard with regard to details of antibiotic resistance patterns in relevant bacteria *in vitro* may be characterised by providing:

- Minimum Inhibitory Concentration (MIC) data of the antibacterial agent against bacterial species likely to be affected, including:
  - MIC distribution data for targeted bacterial species and for relevant non-targeted bacterial species
- Antibiotic resistance pattern details (when available) in relevant human isolates that have emerged with the use of the antibacterial agent, or related substances, overseas and/or in Australia, including:
  - 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.
  - stating whether Australian data are included: provide Australian data if available and recent
- Data on mechanisms of resistance pathways in relevant bacteria
- Estimated rates of development of the expression of resistance, such as indicated from *in vitro* studies of passaged bacteria in the presence of the antibacterial agent.
- *In vitro* cross-resistance data with other antibacterial agents in the same class in targeted and non-targeted bacterial species
- Co-selection of resistance data 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 ICH guidance:
  - CPMP/EWP/2655/99 Points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal product
  - CPMP/EWP/558/95 rev 2 Note for Guidance on Medicinal Products for Treatment of Bacterial Infections
- Evidence concerning the potential for resistant bacteria or resistance transferable genetic elements to spread through the community
- Description of any proposed strategies or recommendations to promote prudent use of the medicine
- Assessment (in terms of the probability categories *negligible*, *low*, *medium*, *high* and *not assessable*) of the probability of exposure to resistant bacteria or resistance transferable genetic elements when the product is used as proposed

Probability categories

- *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

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 bacteria or resistant plasmids in human infections
- The rank-order for the antibacterial medicine with regard to the perceived or known clinical importance of the class of antibiotics in human medicine, based on the Importance Ratings and Summary of Antibacterial Uses in Humans in Australia by Australian Strategic and Technical Advisory Group on Antimicrobial Resistance (ASTAG)

Importance ratings categories

- *High*: Essential antibiotics for treatment of human infections where there are few or no alternatives for many infections (also 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 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 medicine in human health
- Assessment of the impact of disease caused by infections due to antibiotic resistant bacteria (and transferable genetic elements) in humans in the probability 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

Provide an assessment of the uncertainty of data used to characterise the risks (see probability categories) associated with development of resistance to the antibacterial agent (see Risk management – principles and guidelines AS/NZS ISO 31000:2009).

You may use a Risk summary table to summarise the risk characterisation assessment findings.

- Hazard is not categorised
- Place a tick in the risk summary table that characterises the exposure and the impact:
  - For example, if the exposure is low and the impact is negligible, place a tick in the 'low' column for exposure and in the 'negligible' column for impact

Risk summary table

	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 antibiotic resistance
- justification of risk/benefit balance of use of the antibacterial medicinal product in human health in the Australian population

Product Information: resistance prevalence data

Include in the 'Pharmacology' section of the Product Information:

- Australian human antibiotic-resistance prevalence data

Risk Management Plan

In the Australian-specific Annex to the Risk Management Plan (RMP) include:

- 'Resistance' as an ongoing safety concern and a cross-reference to the relevant part of Module 1
- a description of pharmacovigilance activities to monitor for resistance (routine activities and any additional activities); these activities may include ongoing monitoring of resistance at a nominated number of Australian sites
- a description of risk minimisation activities to minimise the risk of resistance (routine activities and any additional activities)

Post-marketing requirements

Following registration:

- Monitor information on the prevalence of resistance in Australia and internationally, for example using:
  - literature reports
  - company data
  - any monitoring activities required as part of the pharmacovigilance plan in the risk management plan
  - other sources including any future national system of surveillance for antibiotic resistance
- Provide such information to the TGA:
  - in Periodic Safety Update Reports, the requirement for which will be described in a condition of registration
  - in applications to update the Product Information at least every five years or more frequently if a signal for antibiotic resistance arises.
- If you identify a signal for newly occurring or increased prevalence of antibiotic resistance, make an assessment of whether the signal constitutes a **significant safety issue**, taking into account factors such as (but not limited to):
  - the pre-existing prevalence of resistance to the antibiotic
  - the volume of use of the antibiotic
  - the indications for use of the product

  For example, the occurrence of resistance to a highly reserved antibiotic used for a life-threatening condition would be considered to constitute a significant safety issue.

- Report significant safety issues relating to antibiotic resistance, according to the timeframes and requirements described in the *Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines*

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication: Guidelines on antibacterial resistance risk data	Drug Safety Evaluation Branch	2007
V2.0	Minor amendment in response to stakeholder comments Editorial amendments	Prescription Medicines Authorisation Branch and Regulatory Guidance Team	March 2017

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R16/253761