

Antibiotic Resistance Review

In line with previous Animal Remedies Board recommendations and working with the Ministry of Health, the first four mass medication antimicrobials (the fluoroquinolones, avoparcin, virginiamycin and avilamycin) causing the greatest human health concern at the time were recently reviewed, and subjected to the process of categorisation.

The reviews were sent out to licensees for their comments prior to being made public. Comments have now been received, and most registrants have responded positively to the decisions.

Background

Antibiotic resistance reviews have been carried out in New Zealand and overseas. The reviews have all emphasised that, while the development of antibiotic resistance is possible (and even likely for particular antibiotics), there is very little factual evidence to:

- clarify the nature and extent of the problem; or
- establish the significance of the use of antibiotics in animals as a source of resistance in human pathogenic bacteria.

In light of the uncertainty surrounding the issue of antibiotic resistance, the Animal Remedies Board considers that the potential for resistance must become a hazard that is addressed when assessing applications for new licences for antibiotic trade name products. The Animal Remedies Board has also directed that the licences of existing antibiotic trade name products be reviewed with regard to the potential to cause antibiotic resistance.

The term ‘antibiotic’ is used comprehensively to include other antimicrobial substances, but does not include disinfectants, sanitisers or sterilisers. (Full details of the expert panel report including definitions are available on the ACVM website.)

1. Purpose of the review

The purpose of the review is to ensure that antibiotic trade name products are adequately regulated in regard to the development of antibiotic resistance in either:

- pathogenic bacteria; or
- bacteria potentially capable of transferring resistance genes to pathogenic bacteria.

2. Expected outcome

It is expected that the licences of all antibiotic trade name products will be adjusted to:

- encourage the prudent use of antibiotics, and
- facilitate the collection of information that could clarify the resistance situation.

This could mean that some licences will be withdrawn entirely or for specific uses or species.

However, in many cases, it is more likely that either:

- no change in a licence is necessary because the controls on the trade name product are already adequate; or
- additional controls will be imposed to achieve the expected outcome.

3. Review rationale

As stated above, there is only limited information available to address the uncertainty as to whether or not the use of antibiotics in animals is contributing significantly to the development of antibiotic resistance in humans. Therefore, until the essential information is available, the rationale for assessing trade name products must be based on qualitative information, experience and an agreed categorisation of the relative importance of an antibiotic in controlling human and animal infections. The rationale to be used for the categorisation is shown in the figure on the following page.

4. Presentation of the conclusions of the review for specific antibiotics

The review describes the categorisation of the above named four antimicrobials reviewed. The Ministry of Health has provided input concerning the human health significance of these substances, and the Animal Remedies Board has addressed the veterinary use hazards and the veterinary health significance, thereby providing the qualitative information needed to apply the review rationale.

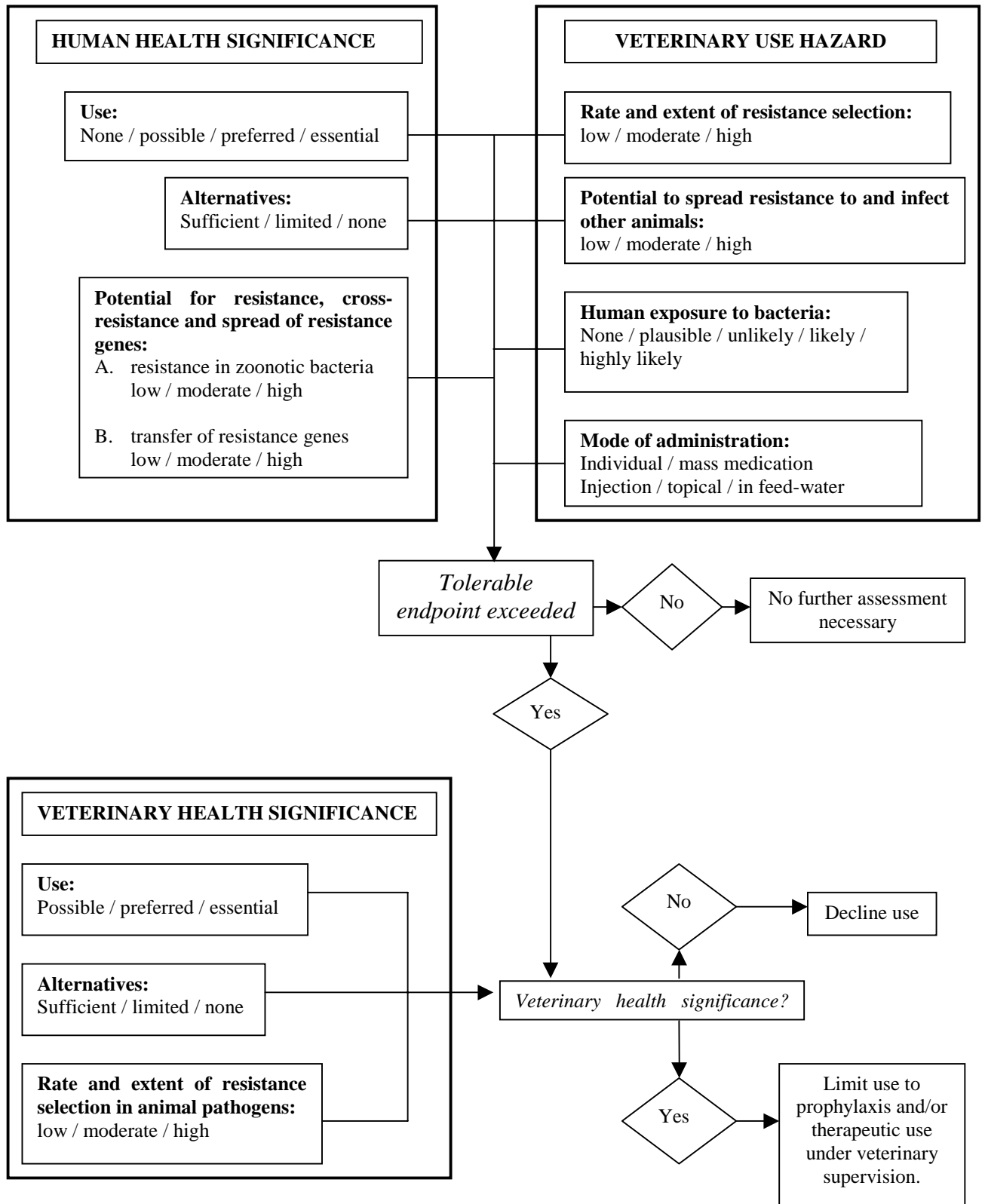
A summary statement is made about each antibiotic in regard to each of the factors in the rationale. The factors have been provided in tabular form as well. The human health significance is a general estimation independent of medicine type or route of administration. The veterinary use hazard and veterinary health significance are estimated relative to the type and use of the product because the risks are significantly different from one type/use to another.

The summary is followed by a statement of the regulatory action to be taken in regard to the licences of trade name products containing the antibiotic. This report will be followed by subsequent reviews of other antimicrobial agents.

5. Process to date

Affected licensees have been advised of the outcome of the review and given an opportunity to comment on the implications for their trade name products.

ANTIBIOTIC RESISTANCE REVIEW RATIONALE



Appendix: Antibiotic Resistance Review

Human Health Significance

The Animal Remedies Board and the ACVM Group felt that specific expertise was required to judge the human health significance of an antibiotic. Therefore, the judgment of the Ministry of Health is used to estimate the significance of an antibiotic in regard to:

- use or expected use in human medicine;
- whether or not alternative antibiotics are readily available and effective; and
- the potential for resistance to develop.

The last criterion is the most complex and subject to considerable uncertainty, particularly in regard to the potential for resistance or cross-resistance to develop in bacteria that might transfer genetic material. There is much more information available about zoonotic pathogenic bacteria such, as *Salmonella* and *Campylobacter* species, so they are considered separately.

Since the uncertainty is relatively high in regard to the potential for resistance to develop, the Animal Remedies Board's policy to act in a prudent manner would prompt regulatory control to protect any antibiotic that is essential (or even preferred) to manage human health problems.

Veterinary Use Hazard

The next consideration is the opportunity for the use of antibiotics in animals to prompt the development of antibiotic resistance in human pathogens. This would require:

- a significant level of use of the antibiotic in animals in a manner that would prompt resistance to develop in animal bacteria and for the resistant bacteria to spread; and
- circumstances in which people would be exposed to the resistant bacteria.

Veterinary Health Significance

The relative significance of an antibiotic in the management of infections in animals helps determine what controls would be necessary and sufficient to protect the use of the antibiotic in humans and, at the same time, allow uses in animals that are essential for their health and welfare.

While emphasis has been placed on the consequential development of antibiotic resistance in human pathogens, the potential for resistance to develop in animal pathogens is also noted.

The following is the antibiotic resistance tolerable endpoint that would prompt regulatory action in regard to the licensing of antibiotic products:

- use of the antibiotic or a related antibiotic in human medicine is at least preferred; and
- there are limited alternative antibiotics for use in human medicine (possibly for a particular purpose); and
- there is at least a plausible mechanism for direct resistance to the antibiotic to develop and the exposure of humans to the resistant bacteria is at least likely; or
- there is at least a plausible mechanism for genomic transfer of resistance to the antibiotic to occur and the exposure of humans to the resistant bacteria is at least likely; and
- the mode of administration of the antibiotic to animals is such that it would increase the probability of resistance developing in a critical mass of the animal population (i.e. mass medication in feed or water exposing whole flocks/herds to the antibiotic); or
- unique circumstances would make exposure of individual people to resistant pathogens likely.

REVIEW OF SPECIFIC ANTIBIOTICS

Fluoroquinolones

HUMAN HEALTH SIGNIFICANCE				
Influencing factor	Estimation			
Use	Preferred-essential			
Alternatives	Limited - none			
Potential to spread resistant organisms	Moderate			
Potential for cross-resistance:				
Resistance in zoonotic bacteria	Moderate - high			
Transfer of resistance genes	Low			
VETERINARY USE HAZARD				
	Oral in feed/water	Injectable	Tablet	Topical
Rate and extent of resistance selection	Moderate - high	Moderate - high	Moderate - high	Moderate - high
Potential to spread resistance to and infect other animals	Moderate - high	Low - moderate	Low - moderate	Moderate - high
Human exposure to bacteria	Likely	Unlikely	Unlikely	Likely
Mode of administration	Mass medication	Individual	Individual	Individual
Tolerable endpoint	Exceeded	Exceeded	Exceeded	Exceeded
VETERINARY HEALTH SIGNIFICANCE				
Use	Possible	Preferred	Preferred	Possible
Alternatives	Sufficient	Limited	Limited	Sufficient
Rate and extent of resistance selection in animal pathogens	Moderate	Moderate	Moderate	Moderate
Veterinary Health Significant	No	Yes	Yes (individual tablet)	No

Human health significance

Ciprofloxacin, and the fluoroquinolones in general, are considered essential antibiotics for treatment of humans. The funding system in New Zealand currently limits access to these antimicrobials to hospital specialists. Fluoroquinolones are predominately used to treat severe infections caused by organisms with limited antibiotic sensitivity, either naturally or through the development of resistance to other commonly available antimicrobials. In the USA increasing resistance has led to fluoroquinolones being recommended as first line treatment in community-acquired pneumonia.

The fluoroquinolones are being used sparingly in human medicine and there are a limited number of alternatives available.

The Ministry of Health believes that various international reports have documented resistance to fluoroquinolones developing in pathogens and commensal organisms in both animals and humans. There is no indication that resistance to fluoroquinolones results in cross-resistance to any other

antibiotic or family of antibiotics. Because of the types of infections that are treated with fluoroquinolones and the circumstances under which they occur, spread of resistant organisms is likely.

Veterinary use hazard

The only fluoroquinolone antimicrobial registered for animal use in New Zealand is enrofloxacin, which is registered for use in New Zealand in companion animals and food animals. Enrofloxacin is a fluoroquinolone, and is rapidly metabolised to ciprofloxacin. It is very closely related to fluoroquinolones used in human medicine, of which ciprofloxacin is an example.

All the animal remedies licensed in New Zealand are intended for therapeutic use in treating infections. There are no growth promotion products, or products intended to be used prophylactically. Enrofloxacin is available in injectable form (companion and food animals), tablet form (companion animals), in-water/fluids (calves), and an application for an aural preparation (companion animals) has been received.

There is reliable evidence of both inherent and acquired resistance to fluoroquinolones in animal pathogens. There has been very little investigation of fluoroquinolone resistance developing in commensal bacteria, but it is reasonable to assume that it is likely.

The potential for spreading resistant bacteria depends on the type of infection. Under intensive farming conditions spread is very likely in gastrointestinal infections. There is considerably less likelihood that the systemic infections being treated would result in significant spread of resistant bacteria.

The mode of administration is also a significant factor. Parenteral (i.e. injectable) administration to individual animals is not likely to result in the spread of resistant bacteria, while oral mass administration to groups of food producing is likely to pose a significant threat of spread. The oral administration of tablets to individual animals to treat systemic infections is not likely to pose a significant threat. Topical administration to ears and eyes is considered to pose a significant hazard to individual people, especially children, when family pets are treated because of direct contact with contaminated discharge from the eyes or ears and the type of bacteria that cause these infections.

Veterinary health significance

Fluoroquinolones are the preferred antibiotic in very specific systemic infections in individual food and companion animals. These specific uses are needed for the welfare of the infected animal because there are very few alternatives. However, even these uses must be under professional control. There are reasonable alternative methods of treatment to the mass medication and topical products.

Conclusion

The use of fluoroquinolones in human medicine must be protected. Some of the licensed animal remedy trade name products (oral-in-water for mass medication and topical in eyes and ears) are considered to jeopardise this use and there are alternative products that can be used. Some licensed products (injectable in individual food and companion animals, and tablets in companion animals) do not significantly jeopardise the use of fluoroquinolones in humans and there are few effective alternatives in the cases in which they would be the preferred treatment. However, these uses must be under professional control to maintain their usefulness and to provide proper advice and follow-up monitoring.

REGULATORY ACTION

Only therapeutic use of fluoroquinolones will be licensed, and only under veterinary prescription. Only injectable products in individual food producing animals and injectable, tablet or topical forms for companion animals, cats or dogs will be licensed. Mass medication uses will not be licensed.

Virginiamycin

HUMAN HEALTH SIGNIFICANCE (Dalfopristin-quinupristin (Synercid))		
Influencing factor	Estimation	
Use	Preferred - essential	
Alternatives	Limited - none	
Potential to spread resistant organisms	Moderate	
Potential for cross-resistance:		
Resistance in zoonotic bacteria	Low	
Transfer of resistance genes	Moderate	
VETERINARY USE HAZARD		
	Oral in feed/water : poultry, pigs, cattle	Oral in feed/water : horses
Rate and extent of resistance selection	Low - moderate	Low - moderate
Potential to spread resistance to and infect other animals	Moderate - high	Moderate
Human exposure to bacteria	Moderate - high through contaminated food	Moderate for individuals
Mode of administration	Mass medication	Individual
Tolerable endpoint	Exceeded	Exceeded
VETERINARY HEALTH SIGNIFICANCE		
Use	Possible	Possible
Alternatives	Sufficient	Sufficient
Rate and extent of resistance selection in animal pathogens	Low	Low
Veterinary Health Significant	Yes (therapeutic use); no (growth promotion)	Yes

Human health significance

Virginiamycin is closely related to the human medicine dalfopristin-quinupristin (Synercid). Dalfopristin-quinupristin (Synercid) has recently been granted Ministerial consent for distribution in New Zealand for the treatment of bacteria resistant to vancomycin. It is considered to be an essential medicine for treatment of humans. Dalfopristin-quinupristin is the current treatment of last resort in multi-resistant organisms. The circumstances under which these organisms cause infections makes spread likely. There are no alternative treatments available.

The potential for resistance or cross-resistance is uncertain. The Ministry of Health refers to the Jetacar report documenting resistance to Synercid having been reported in animals. They believe that the potential to transfer resistant to human organisms is plausible and would, therefore, be of concern to them. They consider virginiamycin to be too important and the uncertainty in regard to whether or not resistance would develop to be too great to dismiss the possibility.

Veterinary use hazard

All but one virginiamycin trade name products for animal use in New Zealand are licensed for growth promotion. The exception is a product used to treat laminitis in individual horses.

There is some evidence of resistance to virginiamycin, but it is uncertain whether it is inherent or acquired. There has been very little investigation of virginiamycin resistance developing in commensal bacteria.

The potential for spreading resistant bacteria depends on the type of infection. Under intensive farming conditions or crowded stable conditions with marginal quarantine or hygiene procedures, spread is likely. The mode of administration is by oral mass medication in pigs and poultry and oral medication of individual horses. Assuming resistance can be acquired, mass medication increases the likelihood of resistance developing. The intensive farming conditions also increase the likelihood of spreading resistant organisms. Contamination of carcasses can occur, so the potential for human exposure to resistant organisms is significant.

The use of virginiamycin in horses is limited to therapeutic treatment of individual horses. It does not pose the same level of risk to the general population, but could expose individuals to resistant organisms. The risk can be managed with adherence to sound professional advice.

Veterinary health significance

The use in individual horses is important for the welfare of horses in certain circumstances. There are alternative treatments in most cases. Accurate diagnosis, antibiotic sensitivity testing and professional advice is essential. The veterinary health significance is considered significant but only moderately so and not at all for growth promotion.

Conclusion

The use of Synercid in human medicine must be protected.

The antibiotic is moderately significant in preventing and treating specific infection in animals, but of negligible significance for growth promotion. The mode of administration and the conditions under which the trade name products are used pose significant risks to sustainable use of virginiamycin in humans. Prophylactic and therapeutic use might be considered to be significant to the welfare of the treated animals, but the products would have to be assessed for these purposes. They would have to be placed under professional control to maintain the usefulness of the antibiotic and to provide proper advice and follow-up monitoring. There are alternative treatments that would not run the risk of jeopardising the human health significance of dalfopristin-quinupristin (Synercid).

The antibiotic resistance risks to people are not as great for individual treatment of horses. However, this use must also be under professional control to maintain the usefulness of the antibiotic and to provide proper advice and follow-up monitoring.

REGULATORY ACTION

Growth promotion use of virginiamycin will not be licensed and existing licences solely for that use will be withdrawn. Prophylactic and therapeutic uses of virginiamycin may be licensed for treatment of individual horses, if the product information provided supports those uses and the uses are subject to veterinary prescription. Mass medication of food producing animals for therapeutic use could be considered, if the product information shows that it is essential for the welfare of the treated animals. If licensed, the use would be subject to veterinary prescription.

Avoparcin

HUMAN HEALTH SIGNIFICANCE	
Influencing factors	Estimation
Use	Essential
Alternatives	Limited - none
Potential to spread resistant organisms	Moderate - high
Potential for cross-resistance	Moderate - high
Potential for Resistance:	
Resistance in zoonotic bacteria	Low
Transfer of resistance genes	High
VETERINARY USE HAZARD	
	Oral in feed/water
Rate and extent of resistance selection	Moderate - high
Potential to spread resistance to and infect other animals	Moderate - high
Human exposure to bacteria	Likely
Mode of administration	Mass medication
Tolerable endpoint	Exceeded
VETERINARY HEALTH SIGNIFICANCE	
Use	Possible
Alternatives	Sufficient
Rate and extent of resistance selection in animal pathogens	Low
Veterinary Health Significant	No (growth promotion) Moderate (prophylactic/therapeutic)

Human health significance

Avoparcin is a glycopeptide antibiotic closely related in structure, mechanism of action and spectrum of activity to vancomycin and teicoplanin.

According to the Ministry of Health, vancomycin and teicoplanin are considered to be essential antibiotics for treatment of humans. Both of these antimicrobials are predominantly used to treat severe infections caused by organisms resistant to other commonly available antimicrobials. Vancomycin and teicoplanin are antibiotics of last resort and there are no real alternatives available. Resistance to vancomycin has been confirmed in both zoonotic and human infections. The potential for transfer to occur is of concern to the Ministry of Health.

Veterinary use hazard

The trade name products for animal use in New Zealand are licensed for growth promotion. There is reliable evidence of resistance to avoparcin and cross-resistance to vancomycin and teicoplanin. Under intensive farming conditions spread of organisms is likely. The mode of administration is by oral mass medication in pigs and poultry. Assuming resistance can be acquired, mass medication of pigs and poultry increase the likelihood of resistance developing. The intensive farming conditions also increase the likelihood of spreading resistant organisms. Contamination of carcasses can occur, so the potential for human exposure to resistant organisms is significant.

Veterinary health significance

Avoparcin has recently been withdrawn from use by the registrant, and production of the antibiotic is ceasing. Alternatives are now being used. The veterinary health significance was considered moderate and not significant for growth promotion.

Conclusion

The future use of avoparcin can cause cross-resistance to antibiotics that are of high human health significance. Products containing avoparcin were licensed for growth promotion use.

The antibiotic was moderately significant in preventing and treating specific infection in animals, but of negligible significance for growth promotion. Alternative treatments that would not jeopardise the human health significance of other antibiotics are now being used.

REGULATORY ACTION

Future growth promotion, prophylactic and therapeutic use of avoparcin will not be licensed and existing licences have been withdrawn.

Avilamycin

Formulation	Oral in- feed
HUMAN HEALTH SIGNIFICANCE	
Influencing factors	Estimation
Use	None (unacceptable therapeutic index)
Alternatives	NA
Potential for cross-resistance	Nil - low
Potential for resistance:	
Resistance in zoonotic bacteria	Low
Transfer of resistance genes	Low
VETERINARY USE HAZARD	
Rate and extent of resistance selection	Low
Potential to spread resistance to and infect other animals	Low
Human exposure to bacteria	Likely
Mode of administration	Mass medication
Tolerable endpoint	Not exceeded
VETERINARY HEALTH SIGNIFICANCE	
Use	
Alternatives	
Rate and extent of resistance selection in animal pathogens	
Veterinary Health Significant	

Human health significance

Avilamycin is an oligosaccharide antibiotic closely related to SCH 27988 (Ziracin), an everninomicin that was in Phase 3 clinical trials for gram positive nosocomial infections in people until May 2000. The manufacturer announced the voluntary discontinuing of clinical development of the everninomicin, an intravenous antibiotic. The agent had been in development for restricted use in a narrow patient population (hospitalised patients with resistant gram-positive infections). The company took this action following review of results from completed Phase II and Phase III clinical studies, which showed that the balance between efficacy and safety did not justify further development of the product.

In light of this recent development, the risk profile concerning the human health significance has changed completely. Even before experimentation was discontinued, the Ministry of Health had no available information about the risk of resistance developing in animal or human models and so could not comment.

The development of cross-resistance with other essential antibiotics is not relevant since the antibiotic will not be used in humans.

Veterinary use hazard

The trade name products containing avilamycin for animal use in New Zealand are licensed for growth promotion. The mode of administration is oral mass medication to pigs and poultry. Mass medication increases the likelihood of resistance developing. The intensive farming conditions also increase the likelihood of spreading organisms. Contamination of carcasses can occur, so the potential for human exposure to organisms is significant. However, there is no indication of cross-resistance or reason to suspect that the use of avilamycin will cause cross-resistance to any antibiotics that are essential to human health. There is also no indication of either inherent or acquired resistance to avilamycin. Therefore, with the present information and the knowledge that avilamycin will not be used to treat people, avilamycin resistance is unlikely to jeopardise the use of any antibiotics that are essential in human health.

Veterinary health significance

Avilamycin is presently used in some intensive farming industries for the prevention of specific diseases. These uses are not recognised in the licences of the products, which are licensed for growth promotion. There are alternative treatments in most cases. For animal health reasons, accurate diagnosis, antibiotic sensitivity testing and professional advice is essential if the antibiotic is to be used for prophylactic or therapeutic purposes. However, this is not relevant to antibiotic resistance in human pathogens.

The veterinary health significance is considered moderately significant.

Conclusion

The use of avilamycin in animals is not likely to contribute to antibiotic resistance in human pathogens. The antibiotic is moderately significant in preventing and treating specific infection in animals, but of negligible significance for growth promotion. While the use of avilamycin to promote growth can be discouraged because it may in the medium to long term reduce the effectiveness of the antibiotic as a prophylactic or therapeutic agent, there are insufficient grounds to withdraw or alter the licences of products intended for that purpose.

REGULATORY ACTION

No action is necessary to alter licences containing avilamycin to manage the problem of antibiotic resistance. However, parties will be encouraged to license products for prophylactic or therapeutic uses instead of growth promotion. Use of antibiotics for growth promotion will be discouraged.