



# Field study in turkeys shows better return on investment of a Tiamutin® + OTC pulse treatment than that of inactivated MG vaccine

## **Introduction**

***The eradication of Mycoplasmas from turkey parent flocks is the best strategy to reduce infections in the progeny. Due to the presence of multi-age fattening flocks as well proximity of other turkey flocks, complete eradication cannot be achieved. Therefore, application of antibiotics is the most economic way of Mycoplasma control.***

A combination of Tiamutin and chlortetracycline demonstrated a 5 times increase of activity against MG and a 4 to 8 times increase of activity against Pasteurella. Challenge trials carried out with the combination of both active ingredients demonstrated a synergistic effect versus *E. coli* as well. It is hypothesized, that the antimicrobial efficacy of both antibiotics is enhanced due to the similar mode of action. Tiamutin and Tetracyclines are both bacteriostatic active antibiotics, that act on the ribosomes and therefore block the protein synthesis of the bacteria.

## **New field data in a commercial turkey flocks in Germany**

Farmers and veterinarians are facing losses in turkey flocks in Germany, due to respiratory disease, caused by mixed infections. Pathologic and serologic evidence demonstrated that besides Mycoplasma, also *Pasteurella*, *E.coli* and *Ornithobacterium rhinotracheale* are involved. Furthermore, after treatment re-infections can occur regularly. This often causes increased mortality, poor feed conversion and costs of medication.

Therefore, a metaphylactic treatment 3 days per month of 165 g Tiamutin 45 % and 200 g active ingredient Tetracyclin per 1000 L water was applied from 5 weeks of age. The performance data of the Tiamutin and Tetracyclin treated flock was compared with a flock that was vaccinated with an inactivated MG vaccine.

## **Clinical and economical results**

Tiamutin and Tetracyclin treatment reduced the respiratory disease signs during the whole fattening period. Furthermore, turkeys remained largely seronegative for MG, while most of the MG vaccinated birds seroconverted 13 weeks after vaccination (i.e. not due to vaccination).

The mortality rates were reduced significantly from 10.4 to 8.4 %. Weight at slaughter was respectively 19.7 and 19.9 kg in the control and study groups. This resulted in an increased return on investment of 1 Euro per turkey.

In conclusion, the combined metaphylactic treatment of Tiamulin and Tetracyclin resulted in less clinical signs, better performance and an increased cost-efficacy over the MG vaccinated control group.

### **Use of Tiamulin and Oxytetracycline for Metaphylaxis of CRD in Turkeys**

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#### **Summary**

In a fattening turkey flock, the poults in one compartment of the house were treated from the 5th to the 16 week of life with tiamulin and oxytetracycline administered in the drinking water for 3 days every 4 weeks for the metaphylaxis of chronic respiratory disease (CRD). At the same time, the animals in the other compartment of the house were vaccinated once with an inactivated *Mycoplasma gallisepticum* (MG) vaccine for chickens. On the basis of the clinical picture, the MG test results, the rate of losses and weight development, the fattening performance in the group, which was given metaphylaxis showed marked advantages over that in the vaccinated control group. The control group had to be given therapy for CRD in the 14th and 16th weeks of life, whereas the study group did not show any respiratory diseases in need of treatment. The laboratory results with the lower frequency of MG detected and the late occurrence of seroconversion shortly before the end of fattening underline the efficacy of the metaphylaxis programme compared with the control group. Apart from the well known efficacy of tiamulin against mycoplasmas, this finding is also explained by the synergistic effect of combination therapy with tiamulin and tetracyclines. This synergistic activity leads to a more effective treatment of infections in poultry resulting from e.g. *Pasteurella multocida* or *Ornithobacterium rhinotracheale*.

It was shown that, in a turkey fattening farm with recurrent MG infections, both the clinical picture and the fattening performance were improved by the use of tiamulin and tetracycline in a strategic metaphylaxis programme. Further therapeutic use of antibiotic substances to combat respiratory diseases could also be avoided, unlike in the control group, so that this metaphylactic programme represents an effective method for improving animal health and performance while at the same time minimizing the long-term use of antibiotics.

#### **Introduction**

Tiamulin has been used for over 20 years in pigs to combat the main target pathogens *Brachyspira hyodysenteriae* and *Mycoplasma hyopneumoniae*. Tiamulin® 45 Water Soluble Granulate is approved in poultry for treatment and prophylaxis of respiratory tract diseases induced by mycoplasmas and complicated by secondary pathogens, such as CRD, infectious sinusitis and synovitis, although little attention has hitherto been paid to these treatment options in Germany. Various studies show the antibiotic activity of tiamulin against MG, *M. synoviae* (MS), pasteurella and ORT- infections (Laber & Schütze, 1975; Baughn et al., 1978; Devriese et al., 2001). The therapeutic treatment of acute mycoplasmosis (MG) was successfully tested in an initial controlled use to determine the efficacy of tiamulin in fattening turkeys in Germany (Schulze & Hamke, 2002). The course of the study was complicated by the occurrence of mixed infections in the form of complicated chronic respiratory disease (CCRD) = and therefore raised the question of the efficacy of earlier, metaphylactic therapy during the incubation period in seroconverting flocks. This should be studied in a further controlled administration in the field.

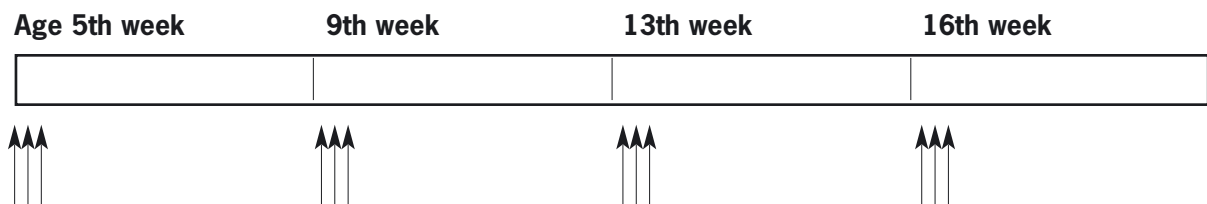
The aim of this study was therefore to investigate the current use of tiamulin (THF) and oxytetracycline (OTC) as practised in North Germany as a strategically applied metaphylaxis programme in turkeys at risk from MG.

### Study design

In a turkey fattening unit, two groups were formed each comprising about 3500 BUT Big 6 type turkey poults in the 5th week of life, when they were transferred to the fattening house and were given different treatments:

### Study group

Fig.1. Metaphylactic treatment programme



70 ppm THF (= 0.007% solution)  
+ 200 ppm OTC (=0.02% solution) for 3 days in each case

or calculated in terms of concentration of active substance per kg bodyweight

8 mg/kg	6 mg/kg	4 mg/kg	3 mg/kg b.w. THF
24 mg/kg	18 mg/kg	12 mg/kg	9 mg/kg b.w. OTC

THF = tiamulin hydrogen fumarate; OTC = oxytetracycline

The animals in the study group were given tiamulin at a dose of 70 ppm (= 165 g Tiamutin® 45 Water Soluble Granulate / 1000 l water) and 200 ppm oxytetracycline (= 1000 g Ursocyclin®/1000 l water) for 3 days via a header tank in the 5th, 9th, 13th and 16th weeks of life. To ensure intake of the full dose, a flavouring agent was added to the drinking water in the form of dextrose at a dose of 200 g / 1000 l drinking water.

### Control group

The control group was given a single subcutaneous injection with the inactivated MG vaccine Poulvac® shortly before transfer to the fattening unit. In Germany, this vaccine is approved for veterinary use in chickens. The use of the vaccine, although not approved for turkeys, was employed in view of the increased airborne infection pressure in a region with a high rate of MG infection amongst turkeys.

As is usual in Germany, the turkeys were fed with a 6-phase feed. Throughout the fattening period, the animals of both stall compartments received a fattening feed containing lasalocid (P 1 – 3) or diclazuril (P4). These coccidiostatic agents, unlike other ionophore coccidiostats (Monensin, Salinomycin, Narasin), are compatible with tiamulin therapy in turkeys. Salinomycin and Narasin also show a high degree of toxicity in turkeys on their own.

## Course of study

### 1. Clinical part

In the veterinary examinations conducted at intervals of two weeks, the T+OTC study group showed no abnormal findings in terms of respiratory symptoms with good flock mobility. In the 6th and 9th weeks of life, symptoms of diarrhoea in equal measure were observed in both house compartments, which were attributable to a mixed infection with *E. coli* and clostridia and, after a resistance test, were treated with antibiotics. In the control vaccinated group, marked symptoms of leg weakness were seen from the 13th week, which increased in the course of fattening.

In the study group, by contrast, only a few individual animals showed lameness. In addition to weakness of the legs, there were marked respiratory symptoms of disease in the control group (dyspnoea, nasal discharge and respiratory noises). In the control group, antibiotic therapy was given in the 14th week of life, which had to be repeated after two weeks because of an increase in respiratory noise. By contrast, animals in the study group up to the 17th week of life showed only minor respiratory noises with good overall health. In the final examination before slaughter the health status of the study group was assessed as good in spite of respiratory noises, whereas the turkeys in the control group showed only average health with marked respiratory noises and lameness. In the comparison of water consumption by the two groups, no differences were observed during the medication.

### 2. Laboratory part

In the 5th, 9th, 13th and 18th weeks of life, blood samples were routinely taken from 20 animals in each group for serological examination for MG and MS. In addition, in the 12th and 15th weeks of life further laboratory tests were carried out to investigate the clinical findings. The blood samples were examined in the rapid slide agglutination test for serological screening. Depending on the results, a follow-up test of the blood samples was carried out by ELISA and / or pathogens determined in tracheal swab samples using PCR.

Table 1. Results of serological tests

Age (weeks– days)	MG			MS		
	RSA	ELISA	PCR	RSA	ELISA	PCR
5-2	S: 0/20 C: 0/20	n.p.	n.p.	S: 0/20 C: 0/20	n.p.	n.p.
9-3	S: 0/20 C: 0/20	n.p.	n.p.	S: 0/20 C: 0/20	n.p.	n.p.
12-0	S: 0/20 C: 0/20	n.p.	n.p.	S: 0/20* C: 10/20*	n.p.	n.p.
13-4	S: 0/20* C: 8/20*	S: 0/20 C: 3/20	S: 3/3 C: 3/3	S: 0/20* C: 10/20*	S: 0/20 C: 0/20	S: 0/3 C: 0/3
15-3	S: 0/20* C: 10/20*	S: 0/20 C: 9/20	n.p.	S: 0/20* C: 16/20*	S: 0/20 C: 2/20°	n.p.
18-1	S: 5/20 C: 10/20	S: 0/20 C: 19/20	S: 3/3 C: 2/3	S: 0/20 C: 0/20	S: 0/20 C: 0/20	S: 0/3 C: 0/3

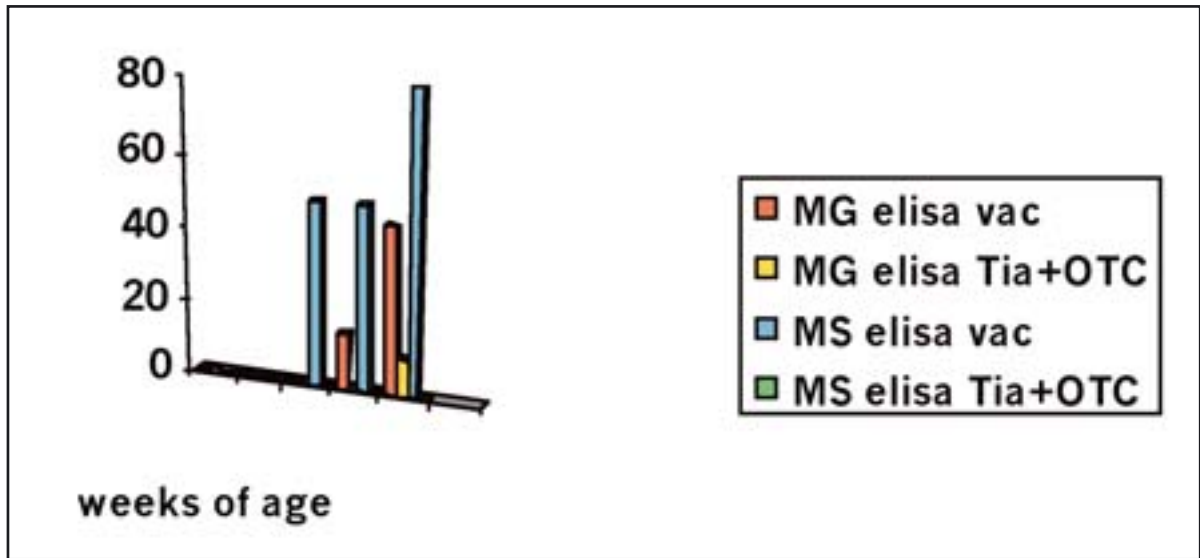
°Titre group 1&2 (non-specific or false positive) S= study group C= control group

Number of positive / number of examined samples n.p. = not performed

\* = significant (p= 0.0001 to 0.0033)

The differences between study and control group are significant in the MG-RSA test in the 13th and 15th weeks of life. In the 12th, 13th and 15th weeks of life, significant differences were observed in MS serology between study and control group.

Graph 1. Proportion positive elisas



### 3. Animal losses

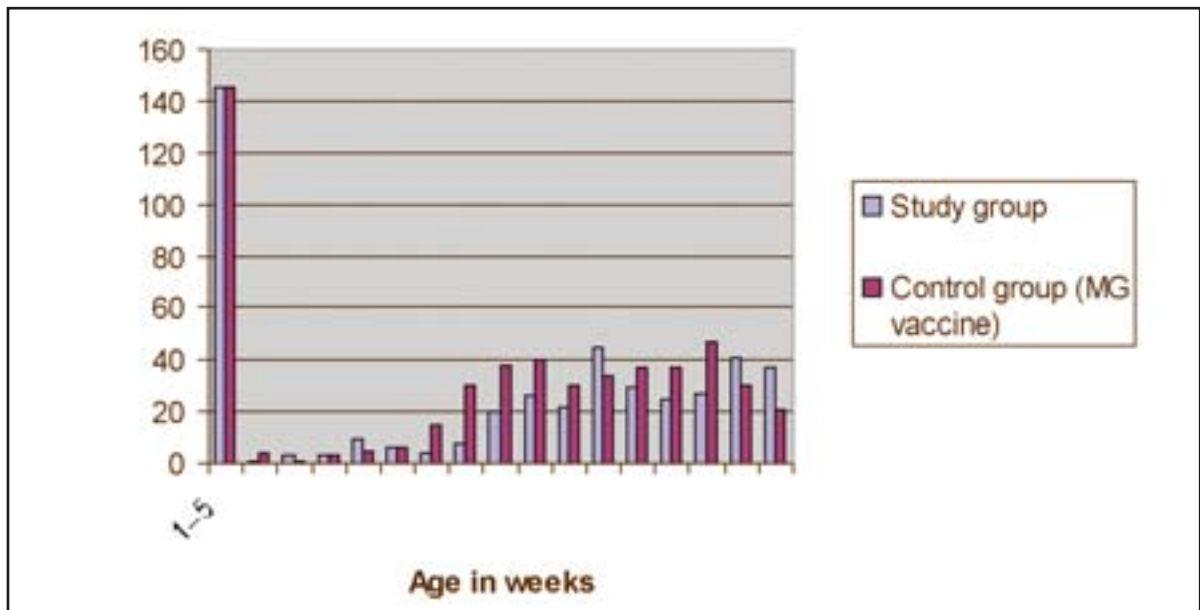
Table 2. Mortality rates from the 5th to 21st week of life

Study stall	Control stall	Difference
8.9	10.9	2.0*

\* significant (at  $p=0.0053$ )

In the period of the study from the 5th to 21st week of life the losses in the group given metaphylactic treatment with tiamulin and oxytetracycline was 2% lower than in the control group, this difference being significant.

Fig. 2. Comparison of the rate of loss during the fattening period

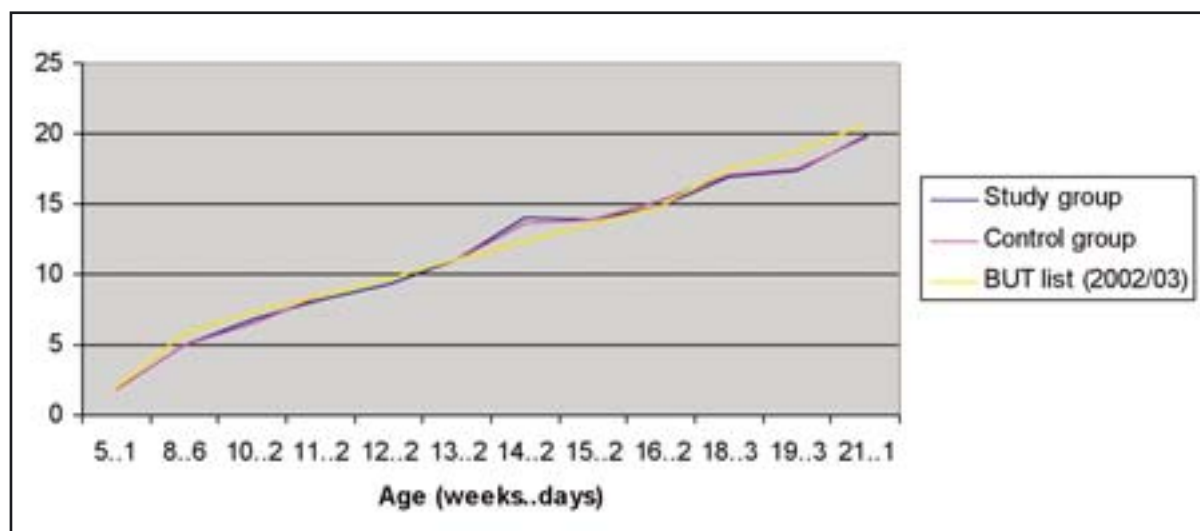


The rate of loss from the 5th to 16th week of life remained at a low level, although here too a difference of 2.1% was seen in favour of the study group. A breakdown of the losses into dead and culled animals showed that markedly more animals in the control group had to be culled for animal welfare reasons. This was predominantly due to the marked symptoms of leg weakness. Over half the losses occurred from age 17 weeks until removal from the stall in the 22nd week of life (study group: 66%, control group: 55%).

#### 4. Weight development

Random samples of 10 to 25 animals per group were weighed every week. The baseline weights from the start of the study were almost identical in the two groups. Overall, the biological performance in the turkey population up to the 17th week of life was rated good. In the further course of fattening, however, the weight development was markedly below requirements, as the following curves show. On slaughter at age 21 weeks and 1 day, the study group had an average weight of 19.9 kg and the control group 19.7 kg. The standard weight at this age lies at 20.7 kg, so that the study group was 3.9% and the control group 4.9% below standard. In this field study, the live weight at slaughter in the group treated with tiamulin/oxytetracycline was 200 g or 1% higher than that in the control group.

Fig. 3 Weight development during the study period (5th-21st week of life)



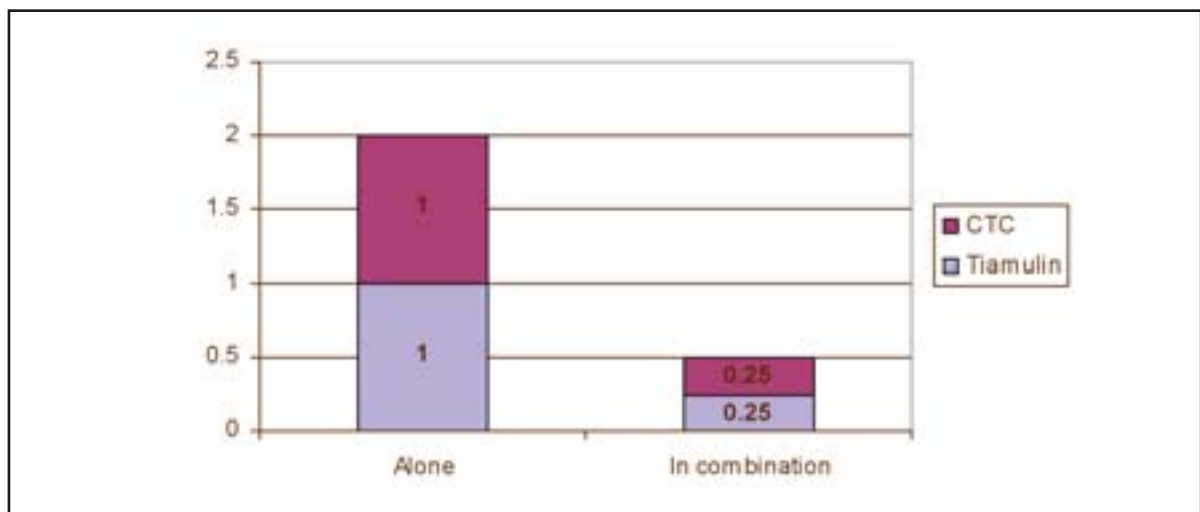
#### Discussion

In this study, the single MG vaccination of turkeys in the rapid serum agglutination test did not result in any measurable seroconversion during the weeks that followed. The single MG vaccination of turkeys with an inactivated vaccine approved for use in chickens cannot prevent a field infection and can only lessen the serious consequences of MG mycoplasmosis to a limited extent. The positive detection of MG in the PCR test in the 13th week of life shows that the study and control group were infected with MG at the same time. This is not surprising in view of the location of the farm in a region with a high density of turkeys, MG field infections in previous inspections on the farm and the spatial proximity of the compartments to each other. Whereas the control group showed signs of seroconversion and clinical symptoms shortly after the infection in the 12th/13th week of life, as expected, it is remarkable that the field infection in the study group did not lead to a measurable seroconversion or to respiratory disease up to the 18th week of life. By contrast, the development of clinical respiratory symptoms and the seroconversion were observed in parallel in the control group. The positive MS results of the rapid serum agglutination test and the ELISA test in the control group are to be seen as non-specific, i.e. a co-reaction as a result of the positive MG findings.

It can be concluded from the clinical course and the MG test results that the metaphylactic treatment programme conducted in the study group was successful: until shortly before the end of fattening, it was possible to confer lasting protection on the study animals against MG infection from outside. Not until the 17th week of life did low-grade respiratory symptoms appear, but these did not require any therapeutic measures. The rate of losses also reflects the positive effect of the metaphylactic, strategic treatment programme: the rate of losses is significantly reduced by 2%, this being attributable in particular to the markedly lower prevalence of lameness symptoms. Apart from the classical symptoms of infectious sinusitis and CRD, infection with MG can also lead in turkeys more often than in chickens to a manifestation in the joints (Siegmann et al., 1993). The inflammatory and exudative processes in joints and tendon sheaths induce arthritis, synovitis and tenovaginitis, which become clinically manifest as mobility disorders, lameness or a massive weakness of the legs with unilateral or bilateral swelling of the hock joints.

In view of the known low MIC values of tiamulin for MG (Lin, 1987; Takahata et al., 1992; Valks & Burch, 2001 & 2002) and the excellent distribution of active substance in the target tissues (respiratory tract and joints) an effective prevention of CRD and leg weakness symptoms could be achieved in this study over several weeks. In addition, the positive effects of the combined administration of tiamulin and tetracyclines must be noted, which have been known for some time in the form of the marked synergistic effect. Apart from widening the spectrum of antibacterial activity, there is also a substantial increase in efficacy. The synergistic effect of these two bacteriostatic antibiotics is achieved through the similar site of action on the ribosome and the prevention of bacterial protein synthesis. In mixed infections of mycoplasmas and gram-negative pathogens such as *P. multocida*, *E. coli* or *O. rhinotracheale*, the results of studies abroad show the advantages of combination therapy with tiamulin and tetracycline (Blagovic et al., 1987; Botarelli et al., 1987; Simon et al., 1988; Stipkovits et al., 1992; Burch et al., 1993; Miller et al., 1996).

Fig. 4. MIC values of *Pasteurella multocida* in administration of tiamulin and chlortetracycline alone and in combination (Burch et al, 1993)



Application of the metaphylactic treatment programme used here is known from studies (Stipkovits et al., 1977) and from administration of the tiamulin/chlortetracycline combination product Tetramutin® which is approved in some European countries (internal data from Novartis Animal Health). The combination therapy carried out here is also economically justifiable in terms of treatment costs.

## Conclusions

The efficacy of tiamulin and oxytetracycline given in combined administration for the metaphylaxis of CRD was demonstrated in a turkey fattening farm in Northern Germany.

With an improvement in the health of the birds there was also an associated lower incidence of the problem of leg weakness. In addition, there was a reduction in the antibiotics used for therapeutic purposes.

From the point of view of animal health, animal welfare and the professional obligations of the veterinarian to protect and restore the health and performance of animals and birds, the metaphylactic treatment programme for strategic use in farms at high risk from mycoplasma infection represents a notable alternative to the “emergency treatment” of acute cases of disease.

**Further information on the Tiamutin® (tiamulin) range of products is available from the Poultry Products Manager at Novartis Animal Health operations in over 50 countries worldwide.**

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