



Rationale for the use of “Tiamutin[®]” Injectable vs *Actinobacillus pleuropneumonia*

“Take home” messages

- Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* continues to be a serious disease in pigs in many countries resulting in losses from mortalities.
- It usually occurs as an acute or peracute condition demanding injectable medication for treatment since feed and water consumption are dramatically reduced.
- The rationale for the use of Tiamutin[®] Injectable for the successful treatment of pleuropneumonia is based on reported data:-
 1. Pharmacokinetic data High concentration in lung tissue, 2x MIC for up to 8 hours post injection
 2. In-vitro sensitivity data Low MIC₉₀ of 4mcg/ml for *App*
 3. Post antibiotic effects Evidence of intracellular antibacterial activity within leucocytes

Evidence of reduction of pathogenicity of *App* at sub-MIC levels
 4. Documented favourable clinical experience in both artificial infection and field studies
- Unlike the recently introduced injectable antibiotic for respiratory infections “Draxxin[®]” (tulathromycin) – Pfizer, Tiamutin[®] Injectable is also highly effective against the life threatening haemorrhagic enteric infections e.g. swine dysentery and acute haemorrhagic enteropathy and has a relatively short withdrawal period.

	Draxxin	Tiamutin
Withdrawal period (in UK)	33 days	10 days

tiamutin[®]
the original – tried, tested, trusted

DEVELOPED EXCLUSIVELY FOR ANIMAL HEALTH • NOT USED IN HUMAN MEDICINE



Pleuropneumonia caused by various serotypes of *Actinobacillus pleuropneumoniae* (*App*) is an important clinical entity in many pig producing countries. It usually occurs as an acute or peracute condition and pigs can die as early as 6-12 hours post- infection.

Feed and water consumption can decrease during an outbreak by as much as 85%. Therefore to be effective appropriate medication must be administered, at least in the early stages of treatment, by injection. Tiamutin® Injection is a preparation which is particularly suitable for the treatment of pleuropneumonia on account of its pharmacokinetic, microbiological and clinical properties. In this MIE the relevant pharmacokinetic and microbiological characteristics will be summarized.

1. Pharmacokinetic properties

At the IPVS Congress, Hamburg 2004, a UK study conducted by Professor Q. McKellar and others was reported. A single intramuscular injection of tiamulin base was administered at a dose of 12.2mg/kg bw (equivalent to 15mg tiamulin hydrogen fumarate/kg bw) to healthy male pigs. The following pharmacokinetic parameters, in respect of concentrations in the lung, colon wall and colon contents were reported:-

Table 1: Pharmacokinetics of tiamulin in target tissues

Parameter	Lung	Colon Wall	Colon Contents
Area under curve (AUC) mcg.h/ml	231.52	64.51	314.23
Area under moment curve mcg.h ² /ml	3868.1	1252.78	9013.0
Mean residence time (hours)	16.71	19.42	28.68
Cmax (mcg/ml)	9.6	2.27	12.75
Tmax (hours)	4.0	6.0	24.0

Constant concentrations in the lungs of tiamulin of approximately 8mcg/ml were achieved between 2 and 8 hours post medication (p.m.). At 32 hours p.m. the concentrations were still greater than 3mcg/ml.

In an earlier U.S study (Anderson M.D. and others, 1994) groups of 5 pigs received intramuscular doses of tiamulin base 11mg/kg bw and 22mg/kg bw (equivalent to 13.6 and 27.2mg tiamulin hydrogen fumarate/kg bw) once daily for 4 consecutive days. On the last day of medication the pigs were killed and the lungs harvested for microbiological assay. (See Table 2)

Table 2: Pharmacokinetics of tiamulin in the lung and colon

Tiamulin activity (mcg/g)			
Parenteral dose (thf) mg/kg bw	Lung	Tonsils	Colon mucosa
13.6	26.9	3.23	2.58
27.2	71.0	8.44	8.99

The results in Table 2 demonstrate that tiamulin concentrated particularly well in the lung tissue in accordance with the dose provided.

2. Microbiological properties

- a) The in vitro sensitivity of *App* to tiamulin has recently been described by Fodor, Stipkovits and Klein at IPVS, Hamburg (2004). 10 field strains of *App* were freshly isolated from the lungs of pigs and identified biochemically. The MIC range, MIC₅₀ and MIC₉₀ figures (mcg/ml) for *App* were as follows:-

Table 3: MICs of tiamulin for *Actinobacillus pleuropneumoniae* (mcg/ml)

MIC range	MIC ₅₀	MIC ₉₀
2.0 - 4.0	2.0	4.0



Casals and others (1990) suggested a “break point” scheme to classify the sensitivity to tiamulin of *App*, as follows:-

Table 4: Breakpoints of tiamulin suggested by Casals and others (1990)

Fully sensitive	Moderately sensitive	Resistant
<8.0mcg/ml	<9-16mcg/ml	>16.0mcg/ml

- b) At IPVS 1998 it was reported by Jacques, M. and others that tiamulin, even at the low concentrations of MIC/2, MIC/4 and MIC/8, markedly reduced the growth of *App*. It profoundly affected the structure of *App*, abnormal long filamentous cells being observed. It was clearly demonstrated that tiamulin even at sub MIC levels can reduce the pathogenicity of *App*. (sub MIC levels of tiamulin are present in the lungs up to 48 hours post injection – see McKellar and others, 2004).
- c) The usefulness of antibiotics in the treatment of bacterial infections can be enhanced if they enter, accumulate and persist in phagocytic cells and inhibit the bacteria which the latter have ingested. Nielsen and Szancer reported at IPVS 1998 that tiamulin penetrated into polymorphonuclear leucocytes at concentrations much higher than the extracellular concentration and remained active intracellularly.

Conclusions

Tiamutin® Injectable (tiamulin base) when administered as a single intramuscular injection equivalent to 15mg thf/kg bw to pigs achieves concentrations in the lung tissue of approx. 8.0mcg/ml between 2 and 8 hours post injection and of 4.0mcg/ml or more up to 24 hours post-injection. These concentrations should be compared with the values for “fully sensitive” strains of *App* for tiamulin and the MIC₉₀ figure for *App* of 4.0mcg/ml (Fodor, Stipkovits and Klein, 2004).

Tiamutin® Injectable concentrates in target tissues such as the lung and a single I/M injection of 15mg thf/kg bw achieves lung levels of 2x the MIC of *App* (MIC₉₀) of 4.0 mcg/ml up to 8 hours post injection. Sub MIC levels of tiamulin have been demonstrated to profoundly reduce the pathogenicity of *A. pleuropneumoniae* and to persist for up to 48 hours post-injection. A further beneficial effect of tiamulin is to concentrate in leucocytes and to remain active intracellularly.

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

List of References

- 1) McKellar, Q. A., Escala, J. and Szancer, J. (2004)
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- 3) Fodor, L., Stipkovits, L. and Klein, U. (2004)
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- 4) Casals, J.B., Nielsen, R. and Szancer, J. (1990)
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- 5) Jacques, M. and others (1998)
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- 6) Nielsen, B.H. and Szancer, J. (1998)
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