Huvexxin®

Pharmacokinetics and PK/PD relationships of Huvexxin® parenteral administration for the treatment of Swine Respiratory Disease (SRD)

Issue

- Successful treatment of respiratory infections can only be achieved by administering of an antibiotic which reaches significant concentrations at infection sites, where bacterial respiratory pathogens are present. Ideally large volumes of the antibiotic are distributed to the target tissues affected and persist in respiratory tissues over a longer period of time.
- What is the relationship between the pharmacokinetic behaviour of tulathromycin (Huvexxin®) following parenteral administration and published data on tulathromycin pharmacodynamics in pigs?

Fact box

- The pharmacokinetic (PK) and pharmacodynamic (PD) relationships of an antibiotic determine its clinical efficacy, which is of most importance for field veterinarians.
- The uptake into alveolar macrophages and intracellular accumulation in phagocytic cells provide a mechanism for sustained delivery of tulathromycin at the respiratory infection site.
- Tulathromycin accumulates intracellularly in porcine macrophages (Intracellular: Extracellular ratio 8:1) and in porcine neutrophils (Intracellular: Extracellular ratio 17:1). [6]
- Tulathromycin exhibits time-dependent antimicrobial effects. Its antibacterial activity is dictated by the length of time that bacteria are exposed to tulathromycin lung concentrations above the MIC.
- Tulathromycin is designed as a full course of therapy against bacterial pathogens associated with swine respiratory disease (SRD) complex, including *Actinobacillus pleuropneumoniae, Pasteurella multocida, Bordetella bronchiseptica,* and *Glaeserella parasuis*.

Fact Sheet

HUVEPHARMA®

Studies

Study 1

Tulathromycin pharmacokinetic parameters and concentrations in blood and lung were determined in pigs after single-dose intramuscular (IM) administration of Huvexxin®. Thirty-six pigs weighing 20.0 to 25.5 kg received a 2.5 mg/kg body weight (BW) dose as a single IM injection. [1]

The maximum tulathromycin concentration in plasma (T_{max}) was achieved within an hour after dosing. Tulathromycin was extensively distributed into the tissue departments, therefore the plasma drug concentrations found were relatively low.

Table 1. Pharmacokinetic parameters of tulathromycin after IM administration in pigs

Pharmacokinetic parameter	Plasma	Lung
T_{max} (hours)	0.25	
C_{max} (µg/ml)	0.62	3.47
Lung elimination half-life $t_{1/2}$ (hours)		142 (approx. 6 days)
Bioavailability (%)	88	

Lung concentrations were consistently higher than those in the plasma. The tulathromycin mean peak lung concentration (C_{max}) was reached within 24 hours post-dosing. Slow release from the lung led to tulathromycin levels above 1.2 µg/g for 10 days.

Table 2. Summary of mean pharmacokinetic parameters following single IM dose to pigs[1]

Time	Plasma (µg/ml)	Lung (µg/g)
Day 1		
(0.5 h)	0.62	---
(12 h)	0.25	2.80
(24 h)	0.15	3.47
Day 3	0.05	2.71
Day 6	0.35	1.70
Day 10	0.02	1.24
Day 15	0.01	0.65

Findings 1

- After rapid release from the injection site and rapid absorption, extensive distribution and slow elimination leads to high and sustained tulathromycin lung concentrations.
- The long half-life results in tulathromycin lung concentrations which remain at levels above 1.2 µg/g for 10 days.
- This increases the exposure time of porcine respiratory pathogens to tulathromycin which potentially optimizes its antibacterial activity.

HUVEPHARMA®

Study 2

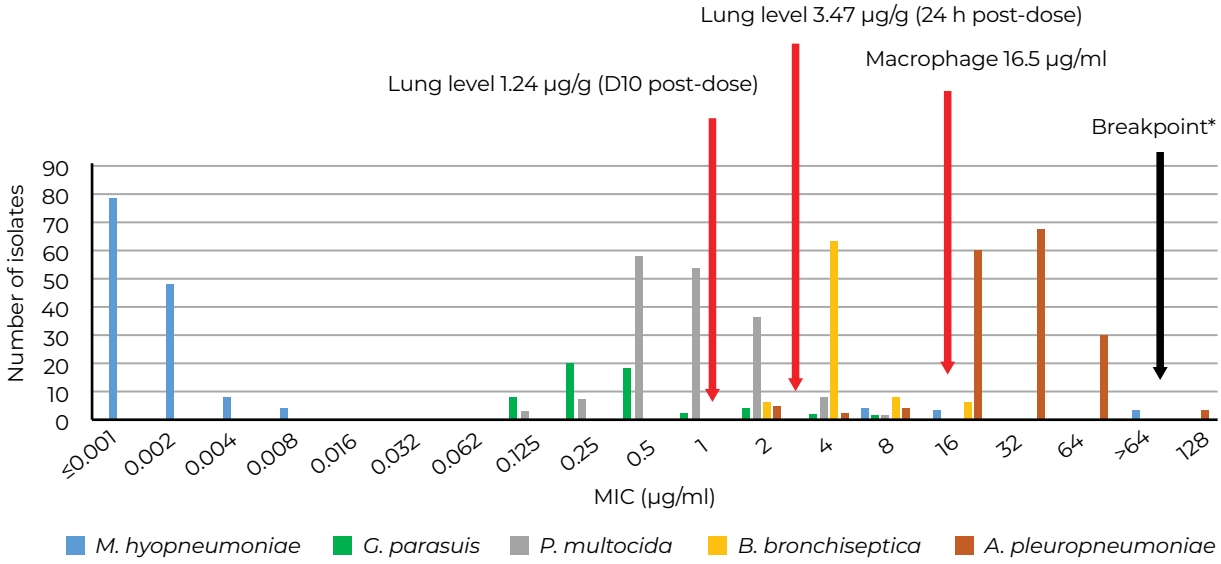
The pharmacokinetic/pharmacodynamic relationships following parenteral administration were studied based on the tulathromycin (Huvexxin®) MIC distributions (µg/ml) for *M. hyopneumoniae, G. parasuis, P. multocida, B. bronchiseptica* and *A. pleuropneumoniae* field strains.[2,3] In total, 610 isolates recovered from SRD cases were used for MIC testing.

Table 3. Minimum Inhibitory Concentration (MIC) values of tulathromycin against different porcine respiratory pathogens

	Publication	№ strains	MIC range	MIC_{50}	MIC_{90}	S (%)	I (%)	R (%)
M. hyopneumoniae	DeJong *et al.* 2020[3]	147	0.002->64	0.062	0.5	---	---	---
G. parasuis	DeJong *et al.* 2023[3]	49	0.12-8	0.25	2	---	---	---
P. multocida	DeJong *et al.* 2023[3]	171	0.12-16	4	8	99.4	0.6	0
B. bronchiseptica	DeJong *et al.* 2023[3]	79	2-16	4	8	100	0	0
A. pleuropneumoniae	DeJong *et al.* 2023[3]	164	2-128	32	64	98.8*		

*Some isolates non-susceptible
S=susceptible, I=intermediate, R=resistant

- The tulathromycin (Huvexxin®) plasma, lung and macrophage concentrations after parenteral administration of tulathromycin at treatment dose are shown in Figure 1.[1,6]



*clinical breakpoints according to CLSI: tulathromycin effective against Pm, Bb ≤ 16 µg/ml, App ≤ 64 µg/ml; resistance ≥ 64. There is no existence of CLSI breakpoints for *M. hyopneumonia.*

Figure 1. Pharmacokinetic/pharmacodynamic relationships following parenteral administration of tulathromycin (Huvexxin®) at a therapeutic dose for the treatment of *M. hyopneumoniae, H. parasuis, P. multocida, B. bronchiseptica and A. pleuropneumoniae*

Findings 2

- Tulathromycin concentrations in lung and alveolar macrophages following parenteral administration at a therapeutic dose exceed MIC values for *M. hyopneumoniae*, *G. parasuis* and *P. multocida* strains tested.
- Macrophage concentrations of tulathromycin are substantially higher than in the lung and play an important role to provide a therapeutic effect against *B. bronchiseptica* and *A. pleuropneumoniae*.[6]
- The clinical efficacy of tulathromycin (Huvexxin®) is linked to uptake and its long release by phagocytes of high therapeutic levels at the respiratory infection site.
- The PK/PD data account for tulathromycin's high efficacy as observed in several efficacy studies. [4,5,7]

Huvexxin® (tulathromycin) demonstrates excellent efficacy against respiratory diseases associated with *M. hyopneumoniae, G. parasuis, P. multocida, B. bronchiseptica* and *A. pleuropneumoniae* following single parenteral administration at a therapeutic dose (2.5 mg/kg BW).

Conclusion

Parenteral administration of Huvexxin® (tulathromycin) at a therapeutic dosage predicts excellent efficacy against respiratory infections caused by *M. hyopneumoniae, G. parasuis, P. multocida, B. bronchiseptica* and *A. pleuropneumoniae*, based on available PK/PD data.

References

[1] Benchaoui, H.A. *et al.*(2004). Pharmacokinetics and lung tissue concentrations of tulathromycin in pigs. J.Vet.Pharmacol. Ther. 27, 203-210. Doi: 10.1111/j.1365-2884.2004.

[2] DeJong, A. *et al.* (2020). Antimicrobial susceptibility monitoring of *Mycoplasma hyopneumoniae* isolated from seven European countries during 2015-2016. Vet Micro, submitted for publication

[3] DeJong, A. et al. (2023). Antimicrobial susceptibility among respiratory tract pathogens isolated from diseased cattle and pigs from different parts of Europe. J.Applied Microbiology, 134, 1-14.

[4] Nanjiani, I.A. *et al.*(2005). Evaluation of the therapeutic activity of tulathromycin against Swine Respiratory Disease on farms in Europe. Vet Therapeutics, Vol.6. No.2, 203-213.

[5] Nutsch, R.G. *et al.* (2005). Efficacy of tulathromycin injectable solution for the treatment of naturally occurring Swine Respiratory Disease. Vet Therapeutics, Vol.6. No.2, 214-224.

[6] Siegel, T.W. *et al.*(2004). Cellular uptake of the triamilide tulathromycin by bovine and porcine phagocytic cells in vitro. J.Anim. Sci, 82 (suppl1): 186.

[7] Waag, T.A. *et al.* (2008). Duration of effectiveness of tulathromycin injectable solution in an *Actinobacillus pleuropneumoniae* respiratory-disease challenge model in pigs. J Swine Health and Production, 16 (3): 126-130

HUVEPHARMA®