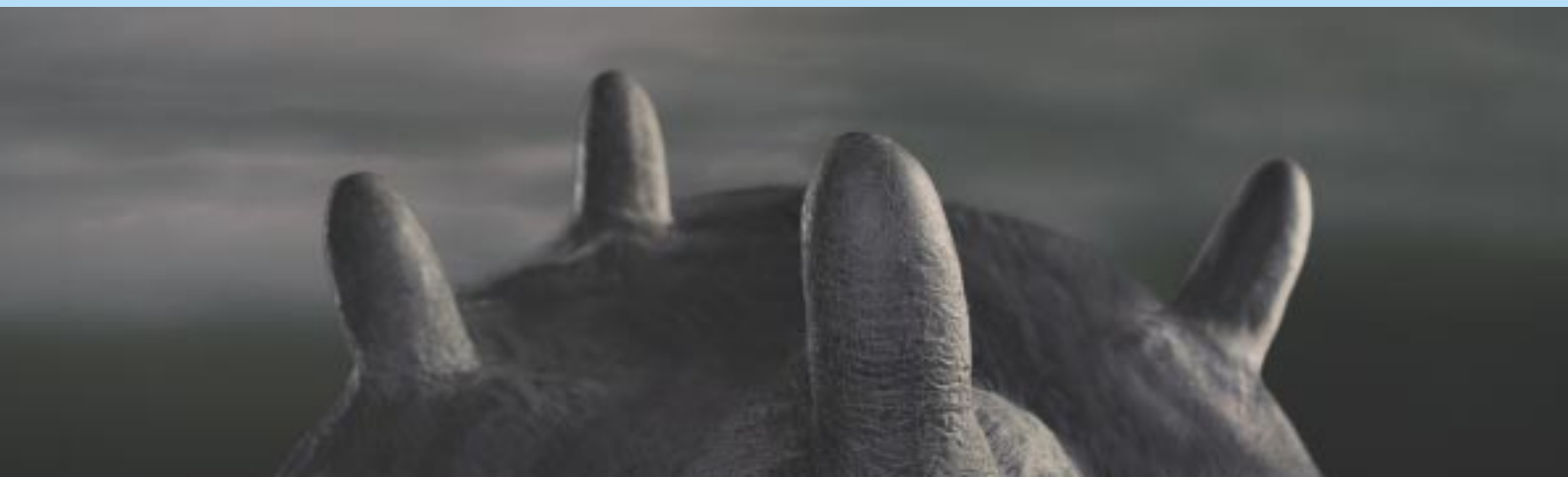


MAMYZIN[®]

INJECTION

TECHNICAL MONOGRAPH



Mamyzin Injection

Penethamate hydriodide

1 Introducing Mamyzin Injection

Staph. aureus, *Strep. uberis*, *Strep. agalactiae* and *Strep. dysgalactiae* together are the most common pathogens isolated from clinical and subclinical cases of mastitis¹. Of these, *Strep. uberis* is one of the most common pathogens identified in VI centres in the UK¹. Penicillin is still widely regarded as the first choice treatment of this infection². *Strep. uberis* gives rise to clinical and subclinical infections in lactating cows where it accounts for high cell counts and poor milk quality. It may also cause subclinical mastitis in dry cows and heifers prior to calving³.

Mamyzin Injection contains penethamate hydriodide, a prodrug of penicillin G which accumulates in high levels in both mastitic and normal milk due to its unique pharmacokinetic profile. It is licensed for the treatment of mastitis caused by penicillin sensitive pathogens.

2 Pharmacokinetics

2.1 Pharmacokinetics in blood

Penethamate hydriodide is a diethylaminoethyl ester of penicillin which, unlike salts of penicillin, is unionised and so exists in a neutral state. It is only weakly water soluble (1% at 20°C) and so forms a suspension in an aqueous environment.

After intramuscular administration, Mamyzin is rapidly absorbed from the site of injection and on entering the blood, penethamate partially dissociates by hydrolysis into penicillin G and diethylaminoethanol (fig 1). At the blood pH (7.2), equilibrium is established where 91.8% of the active drug is present in its hydrolysed form (penicillin G) with the remainder persisting as penethamate. As penethamate leaves the circulation due to its neutral and lipophilic properties and its high affinity to milk (see over), this equilibrium is maintained by re-association of penicillin G and diethylaminoethanol until excretion is complete.

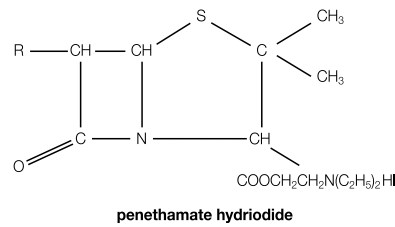
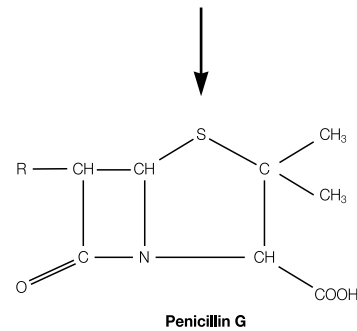


Figure 1



Peak serum levels (measured as dissociated penicillin G) are rapidly reached, 3.76 hours after injection⁴.

2.2 Pharmacokinetics in milk

Following administration of Mamyzin, the un-dissociated penethamate circulates in the blood (pH \pm 7.2) in a non-ionised form. This easily passes over the blood-milk barrier due to the pH gradient present between milk (pH 6.6-6.8) and plasma (pH 7.2) and its weakly basic state (pKa = 8.4). This is further facilitated by its highly lipophilic properties which ease its passage across the lipo-proteinic blood-milk barrier⁵.

Penethamate starts to dissociate as it passes over the blood-milk barrier and this continues during diffusion of the drug through the udder, releasing increasing quantities of penicillin G. The penicillin G is rapidly ionised in the udder (pKa = 2.8) so limiting its return to the circulation. It therefore becomes "trapped" in the udder in increasing concentrations (fig 2). This is described as "ion trapping".⁶

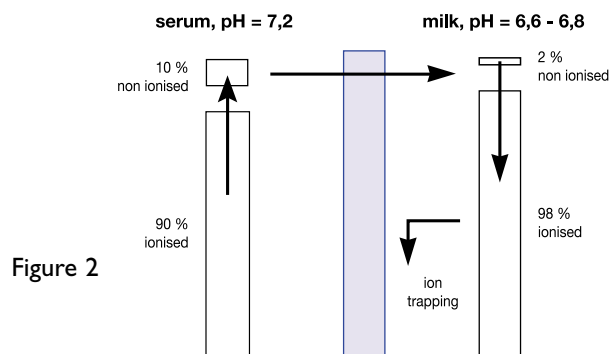


Figure 2

The same pH gradient between blood and milk presides in the presence of mild to moderate udder inflammation such as in cases of subclinical mastitis, thus creating similar pharmacokinetics to those which occur in the healthy udder. In acute mastitis, although the pH of milk is nearer that of blood due to a breakdown of the blood-milk barrier, higher concentrations of penethamate are still to be found in mastitic milk than in blood due to its lipophilic properties⁵.

Not only does un-dissociated penethamate rapidly and easily penetrate the udder whether inflamed or not, but its liposoluble nature gives it a superior aptitude, compared with beta lactam antibiotics such as amoxicillin and aminoglycosides such as streptomycin to diffuse through the parenchyma of the udder, pass into the milk and penetrate the lactogenic cells⁷. It is shown to penetrate the udder eight times faster than penicillin G administered by the intramammary route⁷.

This diffusion through the udder is supported by the mechanism of “ion trapping” discussed above and so explains the milk concentration characteristic of penethamate compared with penicillin G.

After intramuscular injection of Mamyzin in cows, mean maximum penicillin concentrations are achieved in the udder 5.91 hours after injection. This is greater than twice the concentration (mean area under the curve AUC) present in serum⁴. (fig 3)

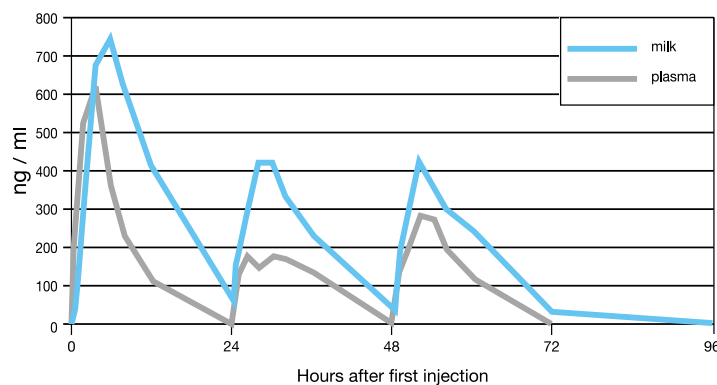


Figure 3⁴: Mamyzin concentration in udder over time

Pharmacokinetic calculations show that whilst the concentration of penethamate in mastitic milk from cows with acute disease may be slightly lower than that in healthy milk and that found in subclinical disease due to the change in milk pH, it is maintained for longer. For example, in work carried out by Ziv⁷ administration of penethamate at the recommended dose provided levels of penicillin in the milk above the MIC of a susceptible pathogen for 24 hours in the milk from cows with acute mastitis compared with 12 hours in normal milk. This compared with a reverse relationship for a number of aminoglycoside antibiotics.

2.3 Metabolism and excretion

After IM injection, all the penethamate is hydrolysed to penicillin G prior to excretion. 40 to 70% is eliminated as penicillin G in the urine, essentially during the first hours after administration. A weak elimination may also take place via bile. That remaining, which is not excreted in the milk, is partially metabolised (30-60%) by hydrolysis of the β -lactam nucleus in the liver to, amongst other derivatives, penicilloic acid and penicillenic acid, both biologically inactive. These are eliminated in the urine.



3 Spectrum of activity and MICs

A range of bacterial agents may cause mastitis in cattle. The most significant include *Streptococcus uberis*, *Streptococcus dysgalactiae* and *agalactiae*, *Staphylococcus aureus*, *Escherichia coli* and *Actinomyces (Arcanobacterium) pyogenes*⁸. Coagulase negative staphylococcus (CNS) and *Corynebacterium bovis* are frequently isolated, however recent work suggests that *Corynebacterium bovis* may be a commensal organism essential for a healthy bacterial equilibrium in the udder of cows⁹.

Penethamate hydriodide is a time dependent bacteriocidal antibiotic with a spectrum of activity primarily against non-penicillinase producing gram+ve cocci. Penethamate is particularly active against streptococci such as *Streptococcus uberis*, *Streptococcus dysgalactiae* and *Streptococcus agalactiae* and penicillin sensitive staphylococci such as *Staphylococcus aureus*.

The Minimal Inhibitory Concentration (MIC) of penethamate (after hydrolysis to penicillin G) is recorded in the literature as follows. (table 1)

Bacteria	N =	MIC 50 (µg/ml)	MIC 90 (µg/ml)	Reference
Non penicillinase producing	NS		0.07	10
<i>Staphylococcus aureus</i>	107	≤ 0.06	0.25	11
	251	0.03	0.07	12
	29	0.06*	0.12*	13
Streptococcus (including	585		≤ 0.07	12
<i>Strep. dysgalactiae</i> ,	48	0.02	0.08	14
<i>Strep. agalactiae</i> and <i>Strep. uberis</i>)				

* modal value instead of MIC 50

N: number of origins tested

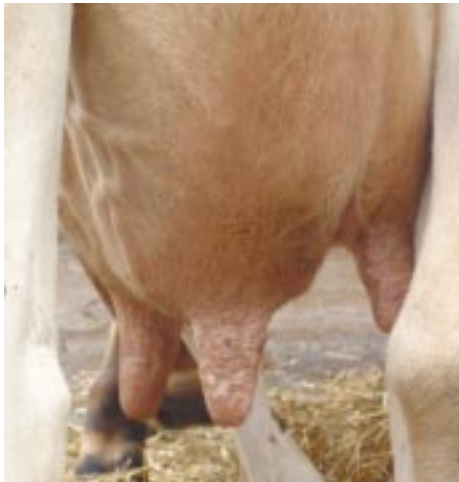
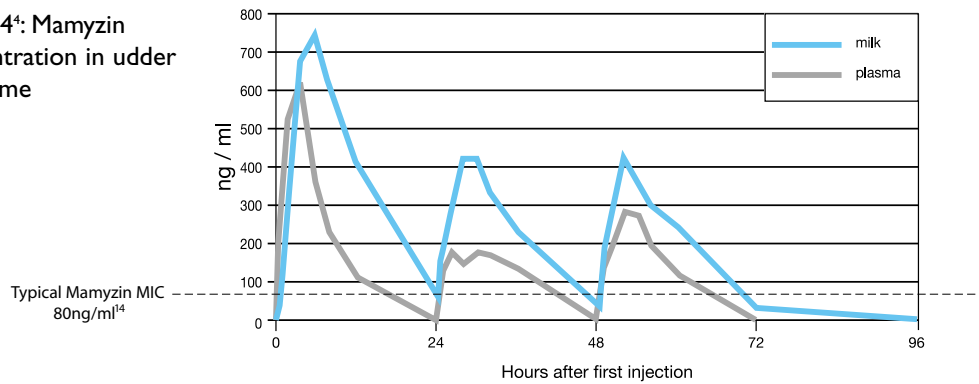
NS: not specified

Table 1: MIC data of penethamate (after hydrolysis) for different mastitis causing pathogens.

The data presented shows that penicillin sensitive staphylococci and streptococci generally have MIC 90 values $\leq 0.07\mu\text{g/ml}$. These data have been collected in a range of European countries and with a value consistently below $0.1\mu\text{g/ml}$ this shows a strong sensitivity of these organisms to penicillin. It is still generally assumed in the UK and Ireland that all isolates of *Streptococcus uberis* are sensitive to penicillin.

Following doses of 15 and 7.5mg/kg, the C_{max} of penethamate in the milk rises to approximately $0.6\mu\text{g/ml}$ and $0.2\mu\text{g/ml}$ respectively⁴. This represents between approximately 3 and 10 times the maximum MIC quoted in the literature. The progress of degradation of penicillin in the udder following administration of penethamate shows that levels above the MIC are maintained for almost 24 hours following each dose⁴.

Figure 4⁴: Mamyzin concentration in udder over time



Acute clinical mastitis



Healthy udder

4 Good clinical practice in the treatment of bovine mastitis

The species of organism isolated from a case of mastitis is central to the choice of antibiotic for treatment and to determining the likely prognosis. The severity of the disease dictates whether the systemic or intramammary, or indeed both, are selected as a route of antibacterial administration or indeed whether supplementary therapy e.g. non-steroidal anti-inflammatory drugs such as meloxicam (Metacam®), are required. It will also determine the likelihood of the animal being seen by a veterinary surgeon or whether it is treated on farm using prescribed treatment protocols.

A recent survey carried out amongst specialist cattle vets from the UK¹⁵ revealed that almost 80% of cows treated for mastitis are treated on farm without veterinary surgeon intervention. Of these cases, 30% are likely to receive parenteral therapy, either alone or concurrently with intramammary therapy. Of those seen by a vet, 85% receive parenteral therapy.

As is quoted in the literature² and dictated by good clinical practice, this survey also revealed that in cases where the species of pathogen is known, a narrow spectrum antibiotic would be the treatment of choice of almost 90% of veterinary surgeon responding.

Despite intensive veterinary use of penicillin in recent years, most gram+ve organisms responsible for mastitis in cattle have shown little increase in resistance to it and the whole group of related antibacterial substances. This is explained by the fact that penicillins do not induce the formation of R plasmids in streptococci necessary for the transmission of the bacterial resistance¹⁶. In the case of mastitis causing streptococci (*Strep. uberis*, *Strep. dysgalactiae*, *Strep. agalactiae*), *in vitro* resistance towards penicillin G appears extremely rare. Today, in the UK, most streptococci isolated from cases of mastitis are considered to be fully susceptible to penicillin G³ yet current therapeutic options result in only a 60% perceived response rate¹⁵. In other countries, the MIC levels are generally low for these organisms confirming high levels of susceptibility^{17,18}.

Although beta-lactamase (penicillinase) does not inactivate penethamate, it does of course inactivate penicillin G, the active product of penethamate. Beta-lactamase producing staphylococci are therefore unlikely to respond to treatment with Mamyzin. According to the literature, there is no evidence that coagulase negative staphylococci isolated from cases of clinical mastitis are resistant to penicillin G.

The efficacy of the antibacterial therapy in the treatment of mastitis due to gram-ve bacteria is uncertain¹⁹. Bacterial self-cure is common with clinical effects being the result of the bacterial endotoxins produced. Non-steroidal anti-inflammatory drugs such as meloxicam (Metacam) are usually indicated. Mamyzin is not indicated for the treatment of *Escherichia coli* induced mastitis.

Whilst clinical mastitis is important both in terms of animal welfare and farm economics, subclinical mastitis is a major source of economic loss on many dairy farms. Losses are due to elevated somatic cell counts (SCC) of infected cows and the associated loss in milk yield^{20, 21}. In addition, when the number of infected cows in a herd is high, bulk milk SCC (BMSCC) may be elevated. This may result in further economic loss because milk quality is monitored by regulatory agencies to determine its suitability for human consumption and penalties on bulk milk with high SCC have been imposed by commercial bottling and processing plants²¹. Treatment of cows with subclinical mastitis is a way to reduce the duration and number of infections, but treatment itself is also a cause of financial loss and is generally considered to be unsatisfactory in 30%¹⁵ of cases treated. The majority of these losses are due to lost production as a result of withholding periods and discarded milk following antibiotic therapy²¹. To be economically viable, the gains of treatment, i.e. the gains resulting from the cure of subclinical mastitis, must offset the losses.

Conclusion

In order to eliminate an infectious agent from a case of mastitis in cattle, it is important that:

- the pathogen concerned is susceptible to the antibiotic chosen
- the distribution of the active ingredient has to be excellent in the targeted tissue i.e. udder and milk
- the concentration of the active ingredient in the udder and/or milk must be above the MIC 90 value
- the duration of treatment must be long enough to achieve both a clinical and bacteriological cure²²

5 The treatment of mastitis in cattle – a desirable outcome

Whilst a positive response of clinical mastitis to treatment can be defined as the disappearance of clinical symptoms such as abnormalities of milk, swelling of the udder, anorexia, reduced milk production, fever etc. it is well recognised that assessment of other non-clinical indicators of disease are also important in determining recovery.

Bacterial cure is defined as the disappearance of the causal organism – identified by culture – which was present at the start of treatment. Usually, two milk samples are collected after the full duration of effect of the antibiotic, taken at 7-10 day intervals. These should be free of the pathogen which was isolated prior to treatment. Since the recurrence of clinical mastitis in individual cows is high, it is likely that this occurs as a result of failure to achieve bacteriological cure despite the disappearance of clinical signs. This poor response in terms of bacterial cure can be attributed to a poor or irregular distribution of the active ingredient throughout the mammary tissue as a result of compression or obstruction of the lactiferous canals by inflammatory swelling. This may also explain why many organisms susceptible to antibiotics *in vitro* do not respond in the field and why prolonged therapy, often given as pulses of treatment so as to remain within the licensed recommendations, is increasingly becoming a treatment option.

Given that mastitis is an inflammatory response to infection or injury, it is valuable to measure other parameters in the laboratory so as to assess the presence of or recovery from disease.

The concentration of somatic cells (SSC) measured in milk correlates with the cellular response to infection in the udder and can be used to define the severity of the inflammatory response and to measure 'cytological' recovery. By definition, since it is a non-clinical parameter, it is valuable in the assessment of both clinical and subclinical disease. A high SSC can be present for a long time even after elimination of the causal infectious agent and whether causing clinical or subclinical disease. Full recovery of the udder cannot be assumed in the presence of a persisting high SCC despite the elimination of clinical symptoms.

In acute inflammation of the udder, the cellular junctions of the tissue are destroyed so allowing chloride ions to leak out and accumulate in the milk. This augments the conductivity of the milk and this can be used as a simple, and often automated, indicator of inflammation and as an indicator of recovery.

6 Mamyzin in the treatment of mastitis

6.1 Clinical mastitis

1. In an open, positive controlled, multi-centre, randomised field study carried out in the East of France^{23, 24} the effects of intramuscular administration of penethamate (three consecutive days) were compared with intramammary treatment, using a cloxacillin/ampicillin combination, in clinical mastitis in lactating cows. The inclusion criteria allowed selection of cases of acute clinical mastitis characterised by abnormal milk, oedema or swelling of the affected quarter and hyperthermia.

The cows in the penethamate group received an intramuscular injection of 10g of penethamate hydriodide on day 1 followed by 5g on the two following days without concurrent intramammary infusion. In the control group, the affected quarters were treated daily for three days with the intramammary infusion containing 200mg of cloxacillin and 75mg of ampicillin without associated parenteral treatment.

Clinical recovery was defined as a return to normal of clinical parameters identified as being abnormal on day 1 and was evaluated on days 2, 3, 8, 17 and 22. Bacteriological recovery was defined as an absence of the pathogen isolated on day 1 (before all treatment) on milk samples taken on day 17 and 22.

In animals infected with *Streptococcus uberis*, the rate of bacteriological cure was equivalent in both groups: 74% after penethamate treatment and 71% in the control group. The rates of recovery with regards to other bacterial species which were isolated (*Staphylococcus aureus*, *E. coli* and CNS) were also equivalent. Overall, the rate of bacteriological cure was shown to be statistically equivalent in both treatment groups ($p > 0.05$), although numerically slightly higher in those in the penethamate group (67% vs. 57%). In cases caused by streptococci, the bacteriological cure rate reached 73% in the Mamyzin treated group. (table 2)

Pathogen

	No. of animals	Cured
Total streptococci spp	30	22 (73%)
<i>Streptococcus dysgalaciae</i>	5	4 (80%)
<i>Streptococcus uberis</i>	23	17 (74%)
<i>Coagulase-negative staphylococci</i>	18	11 (61%)

Table 2: Rates of bacteriological recovery by key pathogen isolated following treatment with Mamyzin

The SCC of the affected quarters decreased in both groups following treatment although there was a higher % of Mamyzin treated cows with QSCC <250,000 on day 17 compared to the control group ($p \leq 0.05$).

Furthermore, there was a more marked reduction in the SCC in all the quarters – whether affected or not by clinical mastitis – after treatment in the penethamate group compared with the animals treated by the intramammary route. A greater proportion of quarters which had a SSC >250,000 cells/ml prior to treatment reduced their count to <250,000 cells/ml on day 17 and 22 ($p < 0.01$). (fig 5)

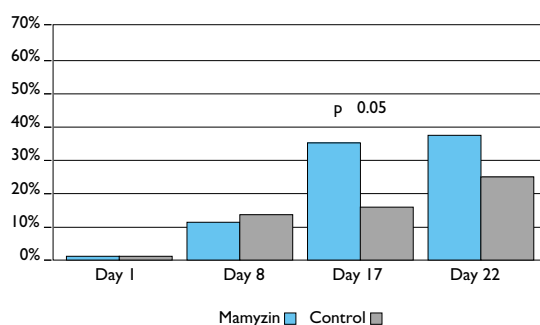


Figure 5²⁴: Proportion of quarters with SCC <250,000 cells/ml as % of those >250,000 cells/ml on day 1 of study

These results show that not only is penethamate useful in treating clinical mastitis, but it gives additional value by treating the subclinical infections which may occur concurrently in adjacent quarters.

2. A recent New-Zealand study compared the rate of clinical and bacteriological cure as well as the effect on SCC of two different protocols used to treat clinical and subclinical mastitis²⁵. Animals were treated with an intramammary infusion of a proprietary preparation containing 1g of procaine benzyl penicillin and 0.5g of dihydrostreptomycin three times at 24 hour intervals or with two intramuscular injections of penethamate (10g then 5g) at 24 hour intervals. 798 cases of clinical mastitis were assessed and *Streptococcus uberis* was the most frequently isolated pathogen. Milk samples were taken 14 and 21 days after treatment for bacteriology and SCC.

The rate of clinical recovery, SCC and the rate of bacteriological cure were comparable between the treatment groups. It was concluded that in the presence of a low incidence of penicillin resistant organisms, penicillin based mastitis therapies are of use in the routine treatment of clinical mastitis.

Mamyzin in the treatment of clinical mastitis – conclusion

In the presence of clinical mastitis caused by *Strep. uberis* or other streptococci as well as penicillin sensitive staphylococci, penicillin is still considered to be treatment of choice. Pharmacokinetic data show that penethamate provides a favourable means of delivering penicillin to treat intramammary infections. Mamyzin provides advantages over intramammary therapy alone in that it effectively controls subclinical disease which may be present concurrently in adjacent quarters.



6.2 Subclinical mastitis

1. A randomised, controlled field trial was performed in 70 milking cows in The Netherlands to determine the therapeutic efficacy of penethamate hydriodide (Mamyzin) against chronic, subclinical streptococcal mastitis during lactation²⁶. Quarter milk samples were collected from subclinical cases of *Streptococcus uberis* or *Streptococcus dysgalactiae* mastitis to determine the effect of treatment on bacteriological cure and decrease of somatic cell count at individual quarter level. Longitudinal data analysis was performed to determine the effect of antibiotic therapy on cow milk SCC, and cow milk yield. Quarters were eligible for inclusion following two consecutive SCCs >500,000 cells/ml and two positive bacteriological analyses carried out at 4 day intervals prior to treatment.

The results in cows receiving penethamate were compared to those in an untreated control group. Bacteriological cure (negative bacteriological analysis 10 and 20 days after treatment) occurred in 59% of affected quarters in the treated group compared with 0% in the non treated control group. Treatment resulted in a significant decrease in SCC at cow and quarter level in comparison to untreated controls. A SCC cure (2 affected quarter SCC <250,000 cells/ml 10 and 20 days after treatment) occurred in 20% of cows in the treated group and 0% in the control group. (fig 6)

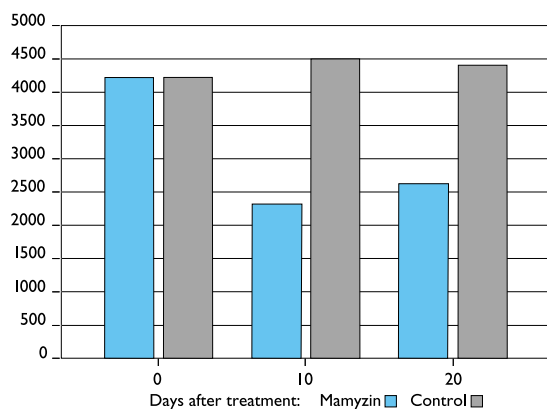


Figure 6²⁶: Mean milk SCC in quarters subclinically infected with *Strep. uberis* or *Strep. dysgalactiae*

Almost 17% of non treated quarters evolved to become clinical while none in the penethamate group evolved into clinical mastitis ($p < 0.05$). Furthermore, none of the untreated quarters recovered spontaneously.

The authors commented that antibacterial treatment of subclinical infections during lactation contributes to prevention of the spread of mastitis in the dairy herds and to the reduction of bulk milk somatic cell counts.

2. In the New-Zealand study cited earlier²⁵ 595 cows presenting with clinical mastitis in several quarters were the subject of investigation of adjacent quarters affected with subclinical disease. The cows with clinically affected quarters were treated with penethamate or with an intramammary infusion containing 1g of procaine benzyl penicillin and 0.5g of dihydrostreptomycin, three times at 24 hour intervals; the adjacent quarters affected by subclinical mastitis in the penethamate group (111 quarters) were defined as receiving treatment whereas those in the control group did not (123 quarters).

In this study, *Streptococcus uberis* was the predominant pathogen and the bacteriological cure rate was significantly greater in the penethamate group compared with the control group ($p < 0.05$).

This emphasises the value of systemic treatment of clinical mastitis, which permits the treatment of both clinically and subclinically affected, and thereby often unrecognised, quarters.

3. It should be recalled that in the French study described above^{23,24} which examined the effect of Mamyzin on clinical mastitis, adjacent non-clinically affected quarters showing SSCs $>250,000$ prior to treatment also showed a significant reduction in SSC following treatment. Treatment of clinically affected quarters therefore brought about a significant benefit in adjacent subclinically, concurrently affected, quarters.

4. A New Zealand case report²⁷ describes a milk quality investigation and the use of Mamyzin on a 550 cow farm where a high number of clinical cases and a rapidly elevating bulk milk cell count was encountered and where *Streptococcus agalactiae* was the causal pathogen. Various milking defects were identified and remedied after which all cows were treated with either intramammary dry cow therapy (Orbenin Enduro® $n=400$) if dry or with Mamyzin ($n=150$) if lactating. The bulk milk cell count fell from the peak of over 800,000 cells per ml over an eight week period to remain below 250,000 cells per ml following the treatment phase.

5. The relationship of antibiotic concentration in the milk to antibacterial efficacy in cows with subclinical mastitis caused by *Staphylococcus aureus* was the subject of a specific study in 1985²⁸. A comparison of penicillin G (procaine salt) and different esters of penicillin G including penethamate was made following the intramuscular administration of each presentation.

The protocol for the administration of penethamate was two or four injections given at 24 hour intervals, each injection corresponding to 5×10^6 IU of penicillin G/cow/day. 62.7% of quarters affected by subclinical mastitis caused by susceptible *Staphylococcus aureus* recovered after two days of treatment compared with 68.8% of affected areas which recovered after four days of treatment.

First lactation cows, or cows with a history of SCCs below 250,000 cells/ml were selected from five dairy herds on the basis of a high SCC ($>250,000$ cells/ml) at their first herd test. Cows were divided into control and treatment groups based on ear tag number. Cows in the control group received no treatment, whilst those in the treatment group received Mamyzin daily for three days. SCC records were assessed for the remainder of the lactation.

Across all cows, treatment with Mamyzin led to a significant increase in the number of animals whose SCC remained below 250,000 cells/ml for the remainder of the lactation (58% vs 25% $p < 0.05$). For first and second lactation animals, treatment with a single course of Mamyzin led to an increase in the number of animals whose SCC remained below 250,000 cells/ml for the remainder of the lactation from 11% in controls to 72% in the treatment group.

6. A randomized controlled field trial²⁹ was performed in France according to GCP involving 161 cows. Cases of naturally occurring subclinical mastitis were treated during lactation with either a three day course of parenterally administered penethamate (n=81) or were left untreated (n=80). The aim of this study was to evaluate the efficacy of penethamate hydriodide treatment on bacteriological cure (BC) and somatic cell count (SCC) evolution at quarter level. Quarters with quarter milk SCC >250,000 cells/ml and with the same bacterial species isolated in two pre-treatment samples two to four days apart were included and milk samples were collected from infected quarters at day 14, day 28 and day 60 post treatment. BC was obtained if the bacterial species isolated prior to treatment was not isolated from the quarter milk samples taken on days 14 and 28 post treatment. Overall BC rate was 60% in the penethamate treated quarters and only 17% in the untreated control quarters (n=151, p <0.001). BC rates of quarters infected with *Staphylococcus aureus*, *coagulase negative staphylococci* or *streptococci spp.* respectively were significantly higher after treatment with penethamate compared with no treatment (p <0.05). The treatment resulted in a significant decrease in SCC at quarter level in comparison with untreated controls over the 2 months observation period. This sustained decrease can be attributed to BC of infected quarters. This study demonstrated that penethamate treatment had a positive effect on BC and SCC in subclinical mastitis during lactation.

7. In five Western Victorian dairy farms sixty nine cows were enrolled in a pilot trial³⁰ designed to investigate the effect of penethamate hydriodide on recently acquired subclinical mastitis. Cows that had an individual cow cell count (ICCC) >250,000 cells/ml at their first or second herd test of the current lactation were enrolled in the trial if they were in their first or second lactation, or if in a subsequent lactation, if they had a history of ICCC <250,000 cells/ml at all herd tests during the previous lactation. Cows were divided into control and treatment group based on ear tag number. The treatment group was treated with penethamate hydriodide shortly after the first or second herd test, and the ICCC of subsequent herd tests were recorded for the remainder of lactation. In 58% of the treatment group and 25% of the control group, all subsequent ICCC were <250,000 cells/ml (p <0.05). If only first and second lactation cows were considered, 72% of the treatment group, and 11% of the control group had subsequent ICCC <250,000 cells/ml (p <0.05). Treatment of these sub-groups of cows within a herd over time may significantly reduce the overall prevalence of high ICCC cows within a herd.

Mamyzin in the treatment of subclinical mastitis – conclusion

In a number of studies, Mamyzin has been shown to be highly effective in the treatment of subclinical mastitis. This has, in most cases, been demonstrated by the positive effects of treatment on somatic cell counts and improvement in milk quality.

6.3 Dry cows and heifers

The effective control of mastitis occurring in heifers is essential if the likelihood of clinical or subclinical infections during the following lactation is to be reduced.

1. In the spring of 2002 a prospective cohort study was carried out on the parenteral use of Mamyzin on heifers pre-calving within a commercial dairy herd in Central Southland, New Zealand³¹.

In the face of an increasing incidence of mastitis in heifers at calving, a treatment protocol involving the use of Mamyzin was initiated for the ensuing season. As a result 35 were untreated (controls) and 54 were treated with 10g of Mamyzin 7 days before expected calving date. If heifers did not calve within 7 days, they received a second treatment (n=3).

There was a significant difference between treatment and control groups in the incidence of mastitis at calving. Heifers treated with Mamyzin had almost half the risk of mastitis as control heifers (RR = 0.49, p = 0.0197). There was no significant difference between groups in mastitis incidence at 7 days post calving.

There was a significant difference between groups in culling levels due to mastitis rate in the Mamyzin treated group. Treatment gave rise to a significant return on investment.

2. A case study was carried out on a 350 cow dairy herd in Italy³² with a problem of *Staph. aureus* infections during the first lactation. It employed a regime of two injections of Mamyzin given to all heifers 24 hours apart, 2 months before calving followed by strict segregation of non-infected heifers from the rest of the herd as identified by the presence of a contaminated milk sample 10 and 20 days post calving.

10% of tested heifers showed positive bacterial contamination of which 81% were coagulase negative staphylococci and 9% were *Staph. aureus*.

Introduction of the strategy gave rise to a decrease in the incidence of *Staph. aureus* infections at calving (20.9% to 6.47%). Preliminary results showed a positive impact on SSC (significant reduction by 45%) and total milk yield (+8.2%).

7 Interactions

Traditionally, penicillin has been used concurrently with many other types of antibiotics to offer a wider spectrum of antibacterial activity. It should be noted however, that since penicillin is a bactericidal antibiotic dependent on bacterial multiplication for effect, it may be neutralised by bacteriostatic antibiotics such as the macrolides and tetracyclines.

8 Conclusion

Mamyzin Injection provides a new, convenient and effective treatment for mastitis caused by penicillin sensitive organisms. It provides persistent and high levels of bacteriocidal penicillin to all 4 quarters following intramuscular injection⁷.

Not only does Mamyzin effectively treat clinical mastitis but it is also effective in the treatment of subclinical disease caused by these same organisms whether occurring alone or concurrently in adjacent quarters to those affected clinically. It is also effective in the treatment of dry cows and heifers providing benefits in the ensuing lactation.





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