CHOOSE BLACK

PROVEN MASTITIS TREATMENTS, TAILOR MADE FOR NEW ZEALAND FARMS.
As you know, the different antimicrobials in mastitis treatments vary in effectiveness against mastitis pathogens. Add to this properties such as vehicle, lipid solubility, degree of ionization and the extent of binding to serum and udder proteins. All play a role in determining the clinical outcome. When we include trial data, bacteriological cure rates, time above MIC, diagnosis of pathogen, farm and individual cow history and the relevant product features, choosing the appropriate mastitis therapy for your clients’ cows becomes a scientific art.

Our mastitis treatments are developed, trialled and made here in New Zealand and contain antibiotics (penicillin, cloxacillin, tylosin) that are especially targeted to the types of mastitis pathogens particularly prevalent in New Zealand.

On one hand we have beta-lactam antimicrobials; these are classified as time-dependant, therefore efficacy is proportional to the time their concentration exceeds the MIC of a particular pathogen. (Whitten and Hanlon, 1997).

On the other, weak organic bases such as macrolides tend to accumulate in milk in the ionized form after parenteral administration and attain concentrations higher than those in blood.

From the table below our range includes treatments for almost every kind of situation, whether an intramammary or parenteral treatment is appropriate.

**CHOOSING THE RIGHT TREATMENT BASED ON THE BEST DIAGNOSIS POSSIBLE ENSURES THE BEST CHANCE OF A CURE.**

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**KEY: SEASON INDICATOR**

These season icons indicate that the related product is a good choice to treat the types of mastitis pathogens that are common at that time of year.

**ADAPTED FROM DCV / NZVA**

<table>
<thead>
<tr>
<th>Streptococcus spp. / Corynebacteria</th>
<th>Staphylococcus aureus* / CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Choice</strong></td>
<td><strong>First Choice</strong></td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td><strong>Route</strong></td>
</tr>
<tr>
<td><strong>Traffic Light</strong></td>
<td><strong>Traffic Light</strong></td>
</tr>
<tr>
<td><strong>Product</strong></td>
<td><strong>Product</strong></td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Cloxacillin</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>Tylosin</td>
</tr>
</tbody>
</table>

**KEY: IMI Intramammary, I/M Intramuscular, Traffic Light**

*Antibiotic Judicious Use Guidelines – Dairy and DCV Formulary

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**YOUR BEST SHOT TO BEAT NEW ZEALAND MASTITIS**
The high dose of penicillin G (1gm) makes Intracillin® 1000 Milking Cow a very effective treatment for the majority of cases of mastitis in dairy cattle caused by gram positive bacteria. In New Zealand, intramammary treatment of Strep. uberis with 1gm of penicillin G has been shown to be very effective, yielding bacteriological cure rates between 70% – 90% (McDougall, 2007). As penicillin is narrow spectrum and has a relatively low MIC for Streptococcus spp, there can be no doubt penicillin is the first choice (DCV Formulary, 2008).

Staph. aureus is beta-lactamase stable and has been shown to be efficacious against Staph. aureus producing this enzyme (Davis and Maplesden, 1975). After intramammary administration, sodium cloxacillin binds to the mammary tissue with a moderate milk:plasma ratio. Cloxacillin is active against gram-positive mastitis pathogens including penicillin-resistant Staphylococci and Corynebacteria. Cloxacillin also has some activity against Streptococcal spp. but is less potent than penicillin.

In New Zealand, Cloxacillin is the first choice antimicrobial for the treatment of mastitis caused by Staph. aureus (DCV Formulary, 2008). Nitroclox™ LA is the only cloxacillin-based intramammary with a registered 3, 4, 5 or 6 x 24 hour treatment regime and is proven locally to be as effective as Orbenin® LA. Nitroclox™ LA provides more milk in farmers' vats, simple milk and meat WHP for both OAD and TAD milking and is made right here in New Zealand.

**MEAN PENICILLIN CONCENTRATION IN MILK AFTER LAST TREATMENT**

- **Intracillin® 1000 Milking Cow**
  - 5 x syringe treatments
  - **96 HOURS**
- **Intracillin® 1000 Milking Cow**
  - 3 x syringe treatments
  - **108 HOURS**

*The only two penicillin-based products registered in New Zealand for combination treatment.

**THE 3 X 24-HOUR TREATMENT REGIME OF NITROCLOX™ LA REMAINS ABOVE THE MIC FOR THE ENTIRE DURATION OF THERAPY**

- **Product**
  - Nitroclox™ LA
  - Orbenin® LA
  - Orbenin® LA
- **Treatment Regime**
  - 3 x 24 hours apart
  - 3 x 48 hours apart
  - 5 x 24 hours apart
- **Total hours out of the Vat**
  - 180 hours
  - 192 hours
  - 192 hours

In New Zealand, Cloxacillin is the first choice antimicrobial for the treatment of mastitis caused by Staph. aureus (DCV Formulary, 2008). Nitroclox™ LA is the only cloxacillin-based intramammary with a registered 3, 4.5 or 6 x 24 hour treatment regime and is proven locally to be as effective as Orbenin® LA. Nitroclox™ LA provides more milk in farmers' vats, simple milk and meat WHP for both OAD and TAD milking and is made right here in New Zealand.

**FLEXIBLE TREATMENT OPTIONS – 24 OR 48 HOUR TREATMENT INTERVALS, FOR ONCE A DAY OR TWICE A DAY MILKING.**

- **3, 4, 5 OR 6 SYRINGES OF NITROCLOX™ LA AT 24 HOURLY TREATMENT INTERVALS HAS A SHORTER MILK WHP THAN THE ONLY REGISTERED TREATMENT REGIME OF ORBENIN® LA.**

**REGISTERED EXTENDED THERAPY CLAIM OF 3 TO 6 TUBES GIVEN 24 HOURS APART, WITH SAME WITHHOLDING PERIODS.**

**YOUR BEST SHOT TO BEAT NEW ZEALAND MASTITIS.**
PenClox™ 1200 High Potency Milking Cow was developed especially for New Zealand conditions. It contains a combination of the two most effective first choice antibiotics for the most common mastitis pathogens in New Zealand – penicillin G and cloxacillin.

The formulation of PenClox™ 1200 High Potency Milking Cow was especially challenging to find. Both components need to be stable to maximise efficacy, shelf life and to have a reasonable milk withholding period. There were over 20 formulations developed and extensively trialled in New Zealand over a 6 year period to find the appropriate carrier, vehicle and base.

PenClox™ 1200 High Potency Milking Cow has flexible 24h treatment regimes, 3 to 6 tubes for once a day and twice a day milking regimes.

In a 2012 NZ study, PenClox™ 1200 was shown to be at least as effective as Mastalone® in the treatment of mastitis. This study, in 30 spring calving herds, showed that treatment with PenClox™ 1200 produced numerically higher bacteriological cure rates than treatment with Mastalone®. A bacteriological cure occurred where the organism(s) present in the Day 0 milk sample did not appear in any of the milk specimens from visits 3, 4 or 5.

In combination these two antibiotics target the major NZ mastitis pathogens. They remain above MIC90 for Streptococcus spp. and Staph. aureus throughout the treatment period.
Parenteral

Parenteral antibiotics can be useful when there are cows with more than one quarter affected by mastitis, in swollen quarters where intramammary may not penetrate well, or in heifers which are unused to having their udders handled.

They can also be used in combination with the intramammary route for severe or difficult to cure cases with Owens et al, 1988 finding higher cure rates for combination therapy compared with intramammary-only treatment.

The times during which antimicrobial concentrations in the mammary gland are effective with parenteral treatment depends largely on the antimicrobial characteristics, dose, bioavailability of the molecule, ability to penetrate mammary gland and susceptibility (Ziv, 1980, Mesterion, 1993).

Tyloguard® RTU

Tylosin is a member of the macrolide group of antibiotics, which inhibit protein synthesis by binding to the 50S ribosome. It is an organic base (pKa = 7.1), moderately bound by serum proteins (40%) and has a high degree of lipid solubility. Due to the ‘pH trap’ phenomenon, tylosin selectively accumulates in areas of low pH such as inflamed udder tissue, and maintains therapeutic levels. It is active against the most common mastitis pathogens isolated from cases of bovine mastitis in New Zealand, Strep. uberis and Staph. aureus. As a first choice for the systemic treatment of Staph. aureus mastitis, tylosin is recommended. At a dose rate of 12.5 mg/kg, milk levels will be maintained in excess of the average MICs for Staphylococci for 24 hours (MacDiarmid, 1978).

Masticillin™ RTU Injection

Masticillin™ RTU Injection is a single shot treatment of high dose micronised penicillin. The micronised penicillin process involves milling, to break up the larger particles, then passing through a mesh to end up with particles of a certain size range. Micronising the penicillin increases the effectiveness as it has more rapid absorption by the animal with greater penicillin concentrations in the udder.

The pharmacokinetic properties of Masticillin™ RTU Injection ensure penetration of the mammary tissue, particularly of inflamed quarters, with high penicillin concentrations being achieved at the site of infection.

Antibiotics which are weak bases attain much higher milk to serum concentrations than weak acids. This doesn’t mean that the weak acids such as penicillin are not effective, however, to achieve high concentrations in the milk from a weak acid parenteral injection you have to inject more antibiotic (ie: 15 million Lu micronised penicillin) than if the antibiotic is a weak base.

The balance between the undissociated material and the dissociated ions - the degree to which the materials separate into its component ions - is influenced by other things which may be present. When bacteria such as Strep. uberis infect an udder they convert lactose to lactic acid – another weak acid – therefore the milk in a mastitic udder is more acidic than normal milk. Also, this acid causes the protein in the milk to clot, a characteristic of mastitic milk.

The presence of this acid alters the undissociated /dissociated balance of the antibiotic and consequently affects the way in which it becomes concentrated in the udder. The weak acid antibiotics are much less affected by the presence of lactic acid, so the net effect is that the difference, in terms of concentrations achieved in the milk, is reduced in cases of mastitis.

Time above MIC₉₀ is the key factor in mastitis cure rates. In an unpublished New Zealand study (data on file), a single shot of Masticillin™ RTU Injection was shown to be above the Strep. uberis MIC₉₀ for at least as long and more consistently than a commonly used 10g + 5g penethamate treatment.

In conclusion, in cases of mastitis the concentration of penicillin in the udder increases while the concentration of penethamate decreases relative to healthy udders.
Comparing apples with apples

One of the key differences between the PenClox™ 1200 study and other published trials is the definition of a bacteriological cure. In the study, the standard for a bacteriological cure was for all 3 post-treatment samples to be clear of the pre-treatment isolate, whereas in the majority of published bacteriological trials a bacteriological cure was recorded only when one or two post-treatment samples were clear of the pre-treatment isolate.

As a guide, there is a loss of approximately 5-10% in apparent cure rate with each negative post-treatment sample, which is borne out in the tables below. In other words, a trial involving three post-treatment samples may show a 10 – 20% lower cure rate than a trial involving only one post-treatment sample, even with the same test product.

Therefore, other trial reports may appear to show a higher bacteriological cure rate because they are based on fewer negative post-treatment samples. The number of negative post-treatment samples is very important when reviewing intramammary efficacy trial data. When only one post-treatment sample is taken, the chances of a negative result from a self-cure are increased, especially if that sample is taken 3-4 weeks after treatment, and consequently the results may not accurately reflect treatment efficacy. The same is also true of the timing of the first sample (e.g. 14 or 28 days versus 7, 14 and 21 days).

Using 3 negative post-treatment samples to demonstrate the efficacy of an antimicrobial treatment in cows with mastitis shows that the bacteriological effects are sustainable over an extended sampling period, therefore the data is more robust as the opportunity for a misleading result is minimised.

### Table 1. Bacteriological cure of New Zealand trial work with three negative post-treatment samples

<table>
<thead>
<tr>
<th>Strain/species</th>
<th>PenClox™ 1200</th>
<th>Mastitax®</th>
<th>PENCLOX™ 1200/5</th>
<th>PENCLOX™ 1200/6</th>
<th>Lactapen G (6 x 12hr)</th>
<th>Lincocin Forte S</th>
<th>Orbenin LA (3 x 48hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>56.4%</td>
<td>74.9%</td>
<td>64.6%</td>
<td>69.7%</td>
<td>40.0%</td>
<td>100.0%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>75.0%</td>
<td>75.0%</td>
<td>51.0%</td>
<td>24.0%</td>
<td>51.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Bacteriological cure of New Zealand trial work with 2 negative post-treatment samples

<table>
<thead>
<tr>
<th>Strain/species</th>
<th>PenClox™ 1200</th>
<th>Mastitax®</th>
<th>PENCLOX™ 1200/5</th>
<th>PENCLOX™ 1200/6</th>
<th>Lactapen G (6 x 12hr)</th>
<th>Lincocin Forte S</th>
<th>Orbenin LA (3 x 48hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>59.9%</td>
<td>82.7%</td>
<td>61.0%</td>
<td>56.1%</td>
<td>41.9%</td>
<td>100.0%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>75.0%</td>
<td>75.0%</td>
<td>51.0%</td>
<td>24.0%</td>
<td>51.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Bacteriological cure of New Zealand trial work with a single negative post-treatment sample

<table>
<thead>
<tr>
<th>Strain/species</th>
<th>PenClox™ 1200</th>
<th>Mastitax®</th>
<th>PENCLOX™ 1200/5</th>
<th>PENCLOX™ 1200/6</th>
<th>Lactapen G (6 x 12hr)</th>
<th>Lincocin Forte S</th>
<th>Orbenin LA (3 x 48hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococci</td>
<td>77.0%</td>
<td>87.0%</td>
<td>59.9%</td>
<td>57.0%</td>
<td>49.0%</td>
<td>100.0%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Streptococcus</td>
<td>75.0%</td>
<td>75.0%</td>
<td>51.0%</td>
<td>24.0%</td>
<td>51.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

The treatment of clinical or sub-clinical mastitis may also be another factor, however a 2007 New Zealand trial of a 1g penicillin intramammary injection found “no sign of significant difference between clinical and sub-clinical cases”. There are a number of other factors to take into account when comparing different studies, such as definition of bacteriological cure, number of post-treatment samples and stage of lactation to name a few, which may make it more demanding to directly compare results.

### Conclusion

Sustainable and efficacious mastitis treatments are a goal for producers and veterinarians alike. Prescribing mastitis treatments involves a rational approach to antimicrobial therapy including analysis of pathogen present, likely susceptibility, antimicrobial penetration, tissue distribution and available treatments.

Proud use of the correct antimicrobial(s) for the pathogen involved based on a veterinary diagnosis is the best approach to retain sustainable therapeutics for the future.

<table>
<thead>
<tr>
<th>ACTIVE INGREDIENT</th>
<th>TREATMENT</th>
<th>TAD MILK WHP</th>
<th>OAD MILK WHP</th>
<th>MEAT WHP</th>
<th>KEY SITUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g penicillin</td>
<td>3 or 6 yrs</td>
<td>96 hours</td>
<td>72 hours</td>
<td>28 days</td>
<td>Calgary or Strip, Strep - ovemia diagnosis</td>
</tr>
<tr>
<td>200 mg cloxacin</td>
<td>3 to 6 yrs</td>
<td>64 hours</td>
<td>120 hours</td>
<td>7 days</td>
<td>Mid late lactation or Strep - abscess diagnosis</td>
</tr>
<tr>
<td>1 g penicillin + 200 mg cloxacin</td>
<td>3 to 6 yrs</td>
<td>24 hours</td>
<td>24 hours</td>
<td>10 days</td>
<td>All lactation</td>
</tr>
<tr>
<td>200 mg/ml tylosin</td>
<td>5 to 10 mg/kg daily up to 5 days</td>
<td>108 hours</td>
<td>120 hours</td>
<td>21 days</td>
<td>All lactation, Multi Quarter</td>
</tr>
<tr>
<td>15 mg i.m. metronidazole</td>
<td>150mg injection in a single dose</td>
<td>108 hours</td>
<td>120 hours</td>
<td>21 days</td>
<td>Calving, Multi Quarter, Heifer</td>
</tr>
<tr>
<td>1 g + 15 mg i.m. penicillin</td>
<td>150mg injection in a single dose</td>
<td>108 hours</td>
<td>120 hours</td>
<td>21 days</td>
<td>All lactation, severe cases</td>
</tr>
</tbody>
</table>
References

Mesterino, N and Errecalde JO. Pharmacokinetic – Pharmacodynamic considerations for Bovine Mastitis Treatment. www.intechopen.com


WT Davis and DC Maplesden (1975). Sodium cloxacillin for Treatment of Mastitis in Lactating Cows.


Restricted Veterinary Medicines. Available only under Veterinary Authorisation. ACVM Nos: A7787, A8037, A10884, A10279, A9713.

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▶ Visit us at CHOOSE BLACK.CO.NZ

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