

TECHNICAL BRIEF



Injection for Cattle (Eprinomectin + vitamin E)

Active Ingredient: Eprinomectin (20mg/ml) and Vitamin E (50mg/ml)

Good things come in small doses™

New NEXEPRIN® MICROJECT™. A unique low-volume combination of eprinomectin and vitamin E in a long acting base designed especially for treatment of adult cattle; including:

- Adult beef cattle
- Lactating and non-lactating dairy cattle
- Breeding animals

NEXEPRIN® MICROJECT™ provides:

- Greater delivery convenience
- Longer persistent activity against a broader range of parasites
- Better blood levels of eprinomectin when compared to topical formulations
- Shorter meat withholding than other macrocyclic lactone injectable formulations

As well as a useful supplementary source of vitamin E.

New Zealand's first low volume cattle injection

Treating adult cattle is never an easy task. NEXEPRIN® MICROJECT™ has been designed especially with that class of animal in mind. The 1mL per 100kg dose rate means that even with the heaviest animal the dose volume is relatively small meaning quicker injection time and less risk of injection site leakage. And each dose delivers a full 200mcg/kg dose of eprinomectin as well as 500mcg/kg of vitamin E.

...and with a nil-milk withholding

NEXEPRIN® MICROJECT™ is also New Zealand's first nil-milk withholding anthelmintic injection, meaning dairy cows can be treated at any stage of lactation.



Eprinomectin - More potent by Injection

Eprinomectin has become a preferred anthelmintic for use in cattle. In particular, it is used extensively in topical formulations for the treatment of lactating dairy cows.

Interestingly however, early development work with eprinomectin demonstrated that when used topically a dose rate of 500mcg/kg was required to eliminate the common mature and immature gastro-intestinal parasites of cattle, while only 56mcg/kg was required when it was administered subcutaneously (Shoop 2001). Given this conclusion it can be seen that NEXEPRIN® MICROJECT™ is effectively delivering a dose 3.5 x (200mcg/kg) the demonstrated dose needed to achieve efficacy via the injection route. While this is not to say that there is a linear relationship between dose and potency there is generally a correlation between higher dose rate and greater efficacy. As a result efficacy is likely to be more assured with NEXEPRIN® MICROJECT™ than it is with a topical formulation of eprinomectin.

It is also worthy of note that Shoop et.al, concluded that eprinomectin was relatively more potent than other macrocyclic lactone anthelmintics injected subcutaneously. While eprinomectin required only 56mcg/kg to eliminate the common mature and immature gastro-intestinal parasite of cattle, these other macrocyclic lactone anthelmintics (abamectin, ivermectin, doramectin and moxidectin) required a full 200mcg/kg dose.

This information suggests that not only is eprinomectin a more potent anthelmintic, it is even more potent when delivered by injection.

The difference is in the blood

The NEXEPRIN® MICROJECT™ delivery system (patent pending) provides improved eprinomectin blood levels when compared to traditional pour-on formulations. To demonstrate this, a bioequivalence study was conducted in which one group of animals were treated with a commercially available eprinomectin pour-on formulation (EPRINEX® Pour-On, Merial) and another group treated with NEXEPRIN® MICROJECT™. Blood samples from both groups were collected over time and analysed for eprinomectin content. Comparative results are presented in Table1 and Figure1.

Table 1: Geometric mean AUC and Cmax values for animals treated with an NEXEPRIN® MICROJECT™ or EPRINEX Pour-on.

Treatment	Mean AUC (SEM)	Mean Cmax (SEM)
NEXEPRIN® Microject™	218.2 ^a (31.1)	40.7 ^a (8.2)
EPRINEX Pour-on	72.6 ^b (10.4)	16.3 ^b (3.3)

a,b = means within a column with different superscript are significantly different from each other.

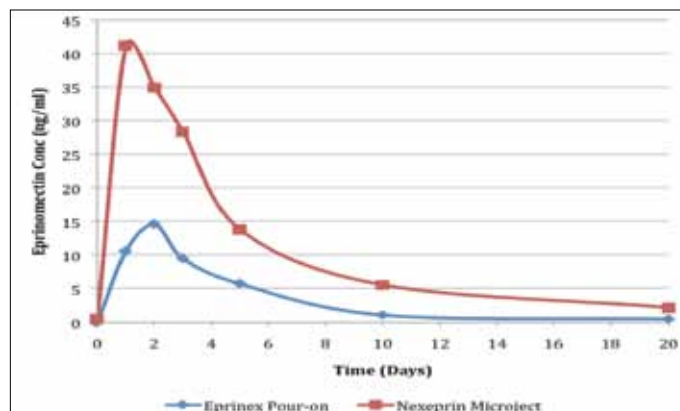


Figure 1: Mean concentration of Eprinomectin in bovine plasma after treatment with NEXEPRIN® MICROJECT™ or Eprinomectin Pour-on.

Faster, Higher, Stronger

In every animal the AUC and Cmax for NEXEPRIN® MICROJECT™ animals were higher than those obtained with animals in the Pour-On treated group. NEXEPRIN® MICROJECT™ was not only absorbed more quickly, but persisted at higher levels for longer.

These results demonstrate the potential for NEXEPRIN® MICROJECT™ to deliver more reliable and consistent parasite control.

This is not only important from the perspective of assuring better dose delivery, but as time progresses and parasite susceptibility to an anthelmintic class decreases a relatively higher more potent dose can be expected to be more efficacious than a lower less potent dose.

So why the addition of vitamin E?

Vitamin E is essential for integrity and optimum function of many biological systems including reproductive, muscular, circulatory, nervous and immune systems.

Some of the symptoms of deficiency in cattle can include poor growth rates, lower feed efficiency and poor fertility.

NEXEPRIN® MICROJECT™ delivers a supplemental dose of 0.5mg of *dl*- α -tocopheryl acetate (equivalent to 0.5 IU of vitamin E) per kg. This could help prevent conditions associated with sub-clinical deficiency at strategic times during the breeding cycle.

The New Zealand Situation

Overseas studies have also associated vitamin E supplementation in cows with increased calf survivability (Persson et.al. 2006). Vitamin E supplementation has also been shown to enhance the immune response of a number of different vaccines (Finch et.al 1996)

It has generally been the view that a high pasture diet is sufficient to supply cattle with sufficient Vitamin E to fulfil their requirements. Yet most of the published New Zealand research dates back to the 1980's and even earlier; a time when supplementary feeding made up a much smaller proportion of the diet of the typical New Zealand cow. But circumstances have changed; herd sizes are now much larger subjecting animals to greater stress, and grain and stored feeds make up a greater proportion of the dietary intake.

In fact more recently Wichtel. et al (1996) drew the conclusion that "it appears that, under certain conditions, New Zealand dairy cattle can become depleted of α -tocopherol to a degree that has been associated with disease in cattle overseas.'

There is no doubt that supplementary feeding now constitutes a large part of the diet of cattle on most modern New Zealand farms. But as Puls (1994) indicates hay or silage generally contains 1/5th the vitamin E found in fresh forage. He also states that high grain diets destroy 40% of vitamin E in the rumen. 'High octane pastures', Palm Kernel

Extract, high nitrate pasture containing potentially higher levels of polyunsaturated fatty acids (PUFA's) increases the requirement for Vitamin E to help prevent oxidative damage.

Given these conclusion it is reasonable to conclude that the changes in feed regimes over the past ten years have probably had significant consequences for vitamin E status.

Are New Zealand cattle routinely significantly deficient in Vitamin E? Probably not.

Are some animals potentially sub-clinically deficient in Vitamin E at certain times? This is a much more likely prospect.

Given the potential risks of loss NEXEPRIN® MICROJECT™ can provide supportive therapy at times when it is most needed and when the cow is most likely to be under stress.

When to use NEXEPRIN® MICROJECT™

NEXEPRIN® MICROJECT™ is suitable for use in animals of any age. NOTE: In younger animals we recommend the use of a combination product such as BOSS® Pour-On or BOSS® Injection.

The PrEE-pare™ Programme

There are key times during the breeding cycle when it becomes even more critical that animals are in peak physical condition. Unfortunately it is at these times when the effect of stress and parasitism can have the most severe impact. The combination of effective eprinomectin-based parasite control and vitamin E supplementation is designed with these circumstances in mind. The PrEE-pare™ Programme provides a set of treatment recommendations for the use of NEXEPRIN® MICROJECT™ and suggests the potential benefits that can result:

PrEE-pare™ Programme		
	Treatment recommendation	Potential Treatment benefits*
Beef Animals		
PrEE-pare for mating	Treat animals immediately prior to mating	Improved fertility & animal condition leading to higher conception rates and tighter calving spans
PrEE-pare for calving	Treat 14-21 days prior to calving	Improved animal condition at calving leading to improved appetite and milk production
Dairy Animals		
PrEE-pare for Dry-off	Treat animals at dry-off	Reduced parasite infection leading to improved feed conversion and animal condition over the early winter period
PrEE-pare for calving	Treat 14-21 days prior to calving	Improved animal condition at calving leading to improved appetite and milk production
PrEE-pare for mating	Treat animals immediately prior to mating	Improved fertility & animal condition leading to higher conception rates and tighter calving spans
PrEE-pare for peak lactation	Treat animals during the first 100 days of lactation	High producing cows, in particular are most susceptible to nutritional stress and parasitism. Treatment at this time can help reduce stress and improve appetite leading to improved milk production

* Actual benefits gained from treatment will depend on factors such as level of parasite challenge, feed availability and type, and vitamin E status.

Product Safety

A clinical safety study was undertaken to determine the safety of NEXEPRIN® MICROJECT™ in the target species. In this study NEXEPRIN® MICROJECT™ was administered to weaned calves (3-9 months of age) at 3 x the recommended dose rate with no adverse effects.

General Information

Active ingredients:

20g/L Eprinomectin and 50g/L Vitamin E

Dose Rate:

1ml/100kg

Indications:

For the effective treatment and control of the following internal parasites of cattle.

Gastrointestinal roundworms:

Adult, Immature and Inhibited L4 Small Brown Stomach Worm (*Ostertagia ostertagi*), Small Intestinal Worm (*Cooperia oncophora* & *Cooperia punctata*). Adult and Immature Barber's Pole Worm (*Haemonchus spp*), Stomach Hair Worm (*Trichostrongylus axei*), Black Scour Worm (*Trichostrongylus colubriformis*), Large Bowel Worm (*Oesophagostomum Radiatum*), Thin-Necked Intestinal Worm (*Nematodirus helvetianus*), Hookworm (*Bunostomum phlebotomum*), Adult: Small Brown Stomach Worm (*Ostertagia lyrata*) and Whipworm (*Trichuris spp*).

Lungworm: Adult and immature *Dictyocaulus viviparus*.

Persistent Activity:

NEXEPRIN® MICROJECT™ administered at 1mL/100kg liveweight prevents reinfection of cattle with the following internal parasites for the time period indicated.

Parasite*	Persistent Activity
<i>Ostertagia spp.</i>	28 days
<i>Cooperia spp.</i>	21 days
<i>Nematodirus helvetianus</i>	14 days
<i>Oesophagostomum radiatum</i>	28 days
<i>Dictyocaulus viviparus</i>	28 days
<i>Haemonchus sp.</i>	14 days
<i>Trichostrongylus spp.</i>	14 days

*The following parasite species are included within each of the relevant genera; *Ostertagia ostertagi*, *O. lyrata*, *O. leptospicularis*, *Cooperia oncophora*, *C. punctata*, *C. surnabada*, *Trichostrongylus axei*, *T.colubriformis*.

Dose table:

1ml/100kg body weight (0.2mg eprinomectin, 0.5mg vitamin E / kg body weight) by subcutaneous injection in the anterior half of the neck.

Bodyweight (kg)	Dose (mL)	500mL Treats
101-125	1.25	400
126-150	1.50	333
151-175	1.75	285
175-200	2.00	250
201-225	2.25	222
226-250	2.50	200
251-275	2.75	181
276-300	3.00	166
300-350	3.50	142
350-400	4.00	125

For cattle over 400kg dose at 1ml/100kg.

Administration method:

Shake well before use. NEXEPRIN® MICROJECT™ is ready to use through standard equipment. Dose the mob to the heaviest animal by liveweight in each group. Do not underdose. Where there is a large variation in size within the group, draft into two or more lines based on bodyweight, to avoid excessive overdosing. Use within 3 months of opening. Do not broach the pack more than 2 times.

Inject NEXEPRIN® MICROJECT™ subcutaneously (under the skin) in the anterior half of the neck. The injection site should be free of surface debris.

A low incidence of soft-tissue swelling at the injection site has been observed. These reactions have disappeared without treatment.

With-holding periods:

14 days - meat, nil - milk (where intramuscular injection may have occurred, animals producing meat or offal for human consumption must not be sold for slaughter during or within 91 days of treatment).

Storage:

The product must be stored below 25°C

Pack Sizes:

500ml pillow packs.

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NEXEPRIN®, MICROJECT™ is registered under the ACVM Act 1997, No. A10854. EPRINEX® is a registered trademark of Merial Limited.

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