NOVARTIS

Recombinant DNA Technology
NUPLURA™ PH is developed with recombinant technology, which results in a consistently pure and uniform antigen preparation. Molecular techniques used to develop NUPLURA PH result in a genetically attenuated leukotoxin antigen that requires no chemical inactivation, which could potentially alter its antigenicity. Additionally, this technology allows for direct and accurate product formulation and potency testing, resulting in a production method that assures the input levels of leukotoxin exceed those which have been proven efficacious. Each serial of NUPLURA PH contains a set level of leukotoxoid based on a direct quantification of the antigen.

Prevention with NUPLURA PH
Effective vaccination with NUPLURA PH can significantly reduce the incidence of BRD. NUPLURA PH is not a simple, inactivated whole-cell product like most other bacterins. It is manufactured using advanced molecular technology and contains outer membrane proteins that have been extracted and purified through a series of steps. The result is a reduction of cellular debris, allowing for a more focused immune response.

A single dose of NUPLURA PH demonstrated protective immunity as early as 10 days after administration. A booster dose can be administered prior to periods of stress or elevated risk of exposure. Safety has been demonstrated in calves 28 days of age and older.

[1]*Data on file, Novartis Animal Health US, Inc.*

Customer Service
(800) 843-3386

www.livestock.novartis.com

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NUPLURA™ PH

Mannheimia Haemolytica Bacterial Extract-Toxoid

For use in healthy cattle, 3 months of age and older, as an aid in the prevention of respiratory disease caused by *M. haemolytica*.

- **Recombinant Leukotoxoid Technology — NUPLURA™ PH** is the first and only cattle vaccine developed in the U.S. market using a combination of outer membrane protein (OMP) and recombinant leukotoxoid technology. NUPLURA PH contains consistent levels of leukotoxoid in every dose to provide a strong immune response.
- **Purified Antigen — NUPLURA PH** is not a simple, inactivated whole-cell product like most other bacterins. It contains outer membrane proteins that have been extracted and purified through a proprietary process. The result is a reduction of cellular debris, which allows the immune system to focus entirely on critical bacterial components.
- **Fast Onset of Immunity — NUPLURA PH** is the only *Mannheimia haemolytica* vaccine demonstrated to deliver immunity in as soon as 10 days.
- **High Degree of Safety —** Demonstrated to be safe for calves as young as 28 days.
- **Minimal Reactivity —** The unique formulation of **NUPLURA PH** is gentle on calves. Administered as directed, there should be no effect on the meat or the carcass at slaughter due to injection site reactions.
- **Ease of Application — NUPLURA PH** does not require mixing or reconstituting. The low-volume dosage of 2 mL is convenient to administer subcutaneously in the neck, following Beef Quality Assurance guidelines.

Product Numbers

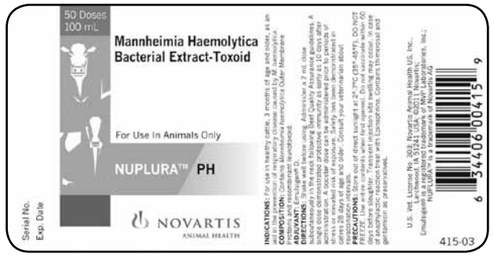
NUPLURA™ PH
#414 - 20 mL — 10 doses
#415 - 100 mL — 50 doses

NUPLURA™ PH

ADJUVANT: Emulsigen® D

DIRECTIONS: Shake well before using. Administer a 2 mL dose subcutaneously in the neck following Beef Quality Assurance guidelines. A single dose demonstrated protective immunity as early as 10 days after administration. A booster dose can be administered prior to periods of stress or elevated risk of exposure. Safety has been demonstrated in calves 28 days of age and older. Consult your veterinarian about revaccination intervals.

PRECAUTIONS: Store out of direct sunlight at 2˚ – 7˚C (35˚ – 45˚F). DO NOT FREEZE. Use entire contents when first opened. Do not vaccinate within 60 days before slaughter. Transient injection site swelling may occur. In case of anaphylactic reaction treat with Epinephrine. Contains thimerosal and gentamicin as preservatives.



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Technical disease information

Mannheimia (Pasteurella) haemolytica is a primary cause of bovine respiratory disease (BRD), also known as shipping fever. It is the bacteria most frequently isolated from pneumonic lungs in cattle and is often associated with acute cases of BRD. *Mannheimia haemolytica* causes respiratory tract infections when the organism is inhaled and transferred into the lungs. Respiratory disease can compound when *Mannheimia haemolytica* is present simultaneously with other infectious pathogens.

Animals are more susceptible to infection and pneumonia caused by *Mannheimia haemolytica* when their natural defenses are compromised due to stress caused by weaning, handling, shipping, commingling or a change in environment. Once inhaled, the bacteria become attached to the lining of the respiratory tract where they colonize, reproduce rapidly and spread throughout the lungs. The severity of disease can depend on the degree of co-infection with associated viral agents such as IBR, PI_3, BVD and BRSV. *Mannheimia haemolytica* is highly transmissible within a herd, particularly when animals are in close contact or crowded environments. The bacteria can be spread by direct contact or through feed and water that has been contaminated by nasal and oral discharges from infected cattle.

Clinical Signs
Mannheimia haemolytica infections can develop and advance quickly. Clinical signs of pneumonia include mild to profuse discharge from the nose and eyes, coughing, high temperatures, lesions on the muzzle and nostrils, edema (fluid) in lower jaw and neck. Animals affected with respiratory disease have difficulty breathing and may be unable to eat or drink. Animals with severe BRD may develop substantial lung lesions that may result in death of the animal. Reduced weight gain is a common and costly effect of BRD in beef cattle operations. Calves can survive infection, but may suffer from irreversible lung damage that is often associated with poor performance.

Protocol:
- 30 Holstein calves between 75 – 83 days of age at vaccination
- One group of 20 vaccinates evaluated for 10-day onset of immunity
- One group of 10 controls receiving placebo
- 2 mL dose of NUPLURA PH subcutaneously in the neck
- 80 mL of challenge administered endoscopically in the bifurcation of the lungs
- Animals observed for clinical signs and examined postmortem for percent of lung tissue with pneumonic lesions

NUPLURA™ PH Efficacy and Safety Data[1]

Table 1. Impact of NUPLURA PH Vaccination on Pneumonic Tissue 10 Days After Vaccination*

Group	N	Mean	Std. Dev.	Minimum	Maximum	*P* Value
Control	10	29.750	18.713	4.610	57.750	—
Vaccinate 10-Day Onset	20	12.282	10.641	0.970	41.3000	0.0024**

* Statistical analysis measured by ANOVA
** Indicates statistical significance at $P \leq 0.01$

Table 2. NUPLURA PH Mitigated Fraction and Associated Confidence Limits

Group	Mitigated Fraction	Lower Confidence Limit	Upper Confidence Limit
Vaccinate 10-Day Onset	69	36.33	100.00

Mitigated fraction is a statistical measure used to determine the relative probability that vaccinated animals will have less severe disease than nonvaccinated animals. Analysis of efficacy data demonstrated that with a mitigated fraction of 69, NUPLURA PH effectively aids in the prevention of pneumonic tissue damage caused by *Mannheimia haemolytica*.

The research proved that NUPLURA PH is safe for use in calves 28 days of age or older. If administered as directed, there should be no effect on the meat of the carcass at slaughter due to injection site reactions (see Table 3).

Protocol:
- Minimum 626 calves at three locations – Iowa, Texas and Utah
- Iowa location included Holstein and Guernsey-cross calves 4 – 12 months of age
- Texas location included beef calves 11 – 13 months of age
- Utah location included Holstein calves 5 – 28 days of age
- 2 mL NUPLURA PH injected subcutaneously in the neck
- Calves monitored for palpable swelling at least 21 days following vaccination
- Calves with injection site swelling > a walnut on Day 21 were monitored again on Day 35

Table 3. Summary of Palpations Recorded for Entire Study

Number of Recorded Observations				
Observation Day	No Swelling	Swelling ≤ size of a pea	Swelling > a pea but < a walnut	Swelling > a walnut
Day 1*	47	46	78	246
Day 2*	64	30	143	181
Day 7	113	53	305	155
Day 21	222	126	261	15
Day 35**	2	5	8	0

* Only the Iowa and Utah sites had injection site paplations recorded on day 1 and day 2.
** Only 15 animals required injection site palpations on day 35 as defined by protocol of continuing to monitor calves with injection sites greater than a walnut at the end of the 21-day study period.