-Flunixin-

Supplemental Information

Flunixin was addressed during the September NOSB meetings held in Washington, DC and it was determined by the board that additional information would be needed. The following information found in this supplement readdresses the seven criteria found in the original TAP report, as well as information regarding the ecological impacts of the drug, the historic use by organic farmers and non-organic farmers, as well as additional information on how flunixin is made.

It should be noted that since the publication of the TAP report done on flunixin, Banamine has been taken off the market and now veterinarians seem to use flunixin produced by a company called Fort Dodge. Regardless of the status of Banamine, flunixin is still the only NSAID allowed for use by veterinarians.[1]

Flunixin is used mostly for veterinary purposes as an analgesic and an anti-inflammatory drug. It persists in inflammatory tissues and is associated with anti-inflammatory properties which extend beyond the period associated with plasma drug concentrations. This has to do primarily with flunixin's counterclockwise spin of light absorption.

Flunixin meglumine, in its drug form, exists for intravenous or intramuscular use in horses and for intravenous use in beef and non lactating dairy cattle only.[2] Unlike in human use, aspirin is not an FDA approved analgesic for veterinary purposes. As a result, flunixin is the only analgesic available on the market today for veterinary use.[3]

How Made:
call tony macee

Historical Use:

Based on information received from a physician who has been working with organic animals in Pennsylvania, the material in question (flunixin) is "the #1 pain reliever in the hands of veterinary practitioners across the country." It is used to medically relieve pain and suffering, whereas butorphanol and xylazine are for surgery. Aspirin has never been approved by the FDA for use in livestock - flunixin has been approved for use in livestock by the FDA (bovine and equine). Both are non-steroidal anti-inflammatory drugs NSAIDs (as are motrin, advil, tylenol, etc.), but the only NSAID approved for livestock is flunixin. Aspirin may reduce fever, but it does not make an animal feel better like flunixin does. Often times, an animal will start to eat within minutes of being given flunixin. Getting an animal to eat (which hasn't been eating) often ends up with the animal 'eating its way' out of whatever is bothering it. If an animal eats, it has a better chance to get better on its own – without potential use of antibiotics and hormones. The benefits of flunixin have been used on rare occasion in an organic animal industry for years.

Action:

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[1] This information was received through a phone call to a veterinarian based in Pennsylvania. He has been working with organic animals for years and his knowledge and information provided proved to be extremely useful.

[2] *"SPAH Product Information: Banamine."* http://usa.spah.com/usa/products/labels/label226.cfm

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Flunixin is a potent non-steroidal anti-inflammatory drug which operates by reducing the biosynthesis of prostaglandins, in particular prostaglandin $F_{2\alpha}$ by inhibiting the cyclo-oxygenase enzymes in the arachidonic acid cascade.[4]

As a Non-Steroidal Anti-Inflammatory Drug (NSAID), some of the anti-inflammatory action of flunixin meglumine appears to be related to its ability to insert into the lipid bilayer of a cell and disrupt normal signals and protein-protein interactions in cell membranes. Inflamed tissues tend to have a lower pH level and NSAIDs are more lipophilic at lower pH. In the cell membrane of neutrophils, NSAIDs inhibit neutrophil aggregation, decrease enzyme release and superoxide generation, and inhibit lipoxygenase.[5]

Flunixin is a drug called a glucocorticoid and "glucocorticoids have two principal physiological effects; metabolic and anti-inflammatory. The metabolic effects include the regulation of protein, carbohydrate, lipid and nucleic acid metabolism. The anti-inflammatory effects are multifaceted and involve many different aspects of the inflammatory response."[6]

Status Among U.S. Certifiers

NOFA: "The following medications are allowed with a 5 day withholding:

- non-steroidal anti-flammatory (i.e. Banamine®)
- antihistamines (e.g. epinephrine, adrenaline)
- anesthetics"[7]

MOFGA: has allowed flunixin in organic animals
NOFA New York: approves
NOFA Vermont: approves
PCO (Pennsylvania Certified Organic): has had flunixin specifically approved for three years now
QAI: does not approve because substance is not listed on OMRI.
Minnesota/Oregon: Go along with the OMRI status. Flunixin is a synthetic drug currently under consideration according to the OMRI.[8]

Section 2119 OFPA U.S.C. 6518(m)(1-7) Criteria

1. *The potential of the substance for detrimental interactions with other materials used in organic farming systems.*

Being that flunixin is used primarily as an NSAID and only by a certified veterinarian, there doesn't seem to be any real issues regarding its toxicity. To be more specific, flunixin is a glucocorticoid drug and it can *only* affect the cellular/energetic system as well as the immune system of animals. Additionally, it has a very short half-life and as a result, it does not exist outside of the animal's body. Therefore, it should not have any detrimental interactions with other materials because it does not exist outside of its drug form in the hands of a certified veterinarian and it is broken down into harmless carbohydrates before released outside of the animal's body.

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[4] *"Flunixin meglumine accelerates uterine involution and shortens the calving-to-first-oestrus interval in cows with puerperal metritis"* Journal of Veterinary Pharmacology Therapy. Volume 24, 2001 pgs. 365-367.
[5] *"Managing Chronic Pain: The NSAIDs"* World Small Animal Veterinary Association. http://www.vin.com/VINDBPub/SearchPB/Proceedings/Pro5000/
[6] *"Glucocorticoid Receptors"* http://www.karobio.com/gr.htm
[7] *VOF Organic Meat & Egg Production – NOFA Vermont* http://www.nofavt.org/sht02_stds7.cfm
[8] Karreman, Hubert J. *PCO POSITION PAPER ON THE USE OF FLUNIXIN, PHENYLBUTAZONE, FUROSEMIDE AND OXYTOCIN IN CERTIFIED ORGANIC LIVESTOCK.*

2. *The toxicity and mode of action of the substance and of its break down products or any contaminants, and their persistence and areas of concentration in the environment.*

According to a 1999 scoring table for veterinary drugs regarding the FSIS Import Residue Plan, NSAIDs besides phenylbutazone (including flunixin) were a given a 4 for *Regulatory Concern*, a 2 for *Withdrawal Time*, a 4 for *Lack of Testing Information on Violation*, a 1 for *New and Existing Human Disease*, and a 3 for *Acute or Chronic Toxicity Concerns*. There was no data found regarding *Historical Testing Information on Violation Reported by the Foreign Countries* and the FSIS themselves did not do any testing for information on violations. The numbers are based on a 1 to 4 scale where 1 = None, 2 = Low, 3 = Moderate, and 4 = High.[9]

The above information provides the understanding that flunixin is, in general, a drug that has not been severely tested and as a result, poses reason for concern when it comes to residue left in meat after the animal has been slaughtered. It is known to have a very short half-life but because of lack of testing, it causes concern.

Generally, flunixin has been declared fairly safe and no real warnings can be found regarding its particular care. However, there are always general precautions that should be taken with any drug. It is advised that the drug not be mixed with other drugs and kept in a container since a dangerous chemical reaction may occur (as in the case with any drug).

As a general guideline for other NSAIDs, it should be stored at room temperature away from moisture and heat.[10] Although specific reports regarding flunixin have not been composed, it may be that the drug becomes flammable when kept beyond its expiration. As a common precaution, drugs should not be stored for longer than their given expiration date. It could become toxic afterwards and could result in unwanted reactions within the body. This, however, is the responsibility of the veterinarian since flunixin is a drug that can only be administered by a certified veterinary physician.

3. *The probability of environmental contamination during manufacture, use, misuse, or disposal of the substance.*

As aforementioned, there are no apparent dangers about flunixin or flunixin meglumine listed because of its short half life, therefore, the probability of environmental contamination is low. As a general precaution regarding all NSAIDs, these drugs should be stored at room temperature and away from heat. Additionally, they should not be kept beyond the expiration date due to chemical composition and reactions that could take place over shelf time. It is possible that the drug may become flammable if kept after expiration date.

4. *The effects of the substance on human health.*

A significant amount of tests were conducted to determine how safe flunixin meglumine residues were to human blood. It was found and determined that the human liver was the target tissue and therefore an adequate withdrawal time of 4 days should follow intravenous injections of 2.2 mg/kg administered for up to three days.[11]

"Non-steroidal anti-inflammatory drugs (NSAID) are widely used in both human and veterinary medicine because they suppress or reduce inflammation, pain, swelling, heat, hyperemia, and loss of bodily function caused by various forms of arthritis. Prolonged use of NSAID is discouraged because possible side effects include gastric intestinal ulceration that can sometimes be accompanied by anemia and disturbances in platelet function. A 1992 survey of 2000 veterinarians whose practices were devoted to at least 50% dairy

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[9] Table 5.1: Scoring Table for Veterinary Drugs; 1999 FSIS Import Residue Plan

[10] *More about NSAIDS (non steroidal anti-inflammatory drugs), with questions and answers* http://www.livingwith.co.nz/index.cfm/area/Medicines/Disease/Osteoarthritis/document/287#Who%20should%20NOT%20take%20NSAIDs%3F

[11] "*Banamine. Research Background*" http://63.236.84.42/research/bfmsic.html

and beef cattle, revealed that approximately 88% (1,146/1,306) of the respondents prescribed NSAID in combination with antibiotics. Flunixin meglumine (FX) and phenylbutazone (PB) are two NSAID that are not permitted for lactating dairy cows. Our FY01 research produced a rapid screening method for flunixin meglumine (FX) and phenylbutazone (PB) residues in raw milk. For the test, raw milk is directly applied to Neogen® Corporations FX and PB ELISA (enzyme-linked immuno-sorbent assay) kits. The kits are sensitive in the low part-per-billion range (0.5ppb FX and 5ppb PB) in milk." [12]

5. *The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.*

Once again, flunixin does not exist in its drug form outside of the veterinarian's supervision. It has a very short half-life, and as a result, the animal's body breaks it down to harmless carbohydrates and it exits the body through the animal's urine. Therefore, there are no real biological and chemical interactions of flunixin outside of the animal's body because it does not exist in its form.

In its injectable form, the following animals have been tested to see their reaction to flunixin:

According to findings provided by the NIH, flunixin meglumine can be used on mice, rats and rabbits without causing particular harm to them.

For cats, however, flunixin as well as other anti-inflammatory drugs have been proven very dangerous. It has been noted that cats can suffer from bone marrow depression, gastric lesions, anemia, and even death because of NSAIDs since aspirins, in general, are toxic to them.

For dogs, NSAIDs should be used with caution: acetaminophen and ibuprofen are contraindicated while aspirin dosages should be cautiously regulated.[13]

With regards to horses and cattle, flunixin comes with very specific guidelines for administration that should be followed by the certified veterinarian.

6. *The alternatives to using the substance in terms of practices or other available materials.*

In the veterinary world, flunixin is the *ONLY* NSAID allowed for animal use. Aspirin has not been FDA approved and while butorphanol and xylazine are used for surgical relief, flunixin is the only pain-reliever allowed for animal use by a veterinarian. As a result, there are no real alternatives although there has been research done on the following drugs considering their effective pain relief components:

A study was conducted comparing the clinical efficacy of 3 NSAID's used in conjunction with ceftiofur for treatment of bovine respiratory disease. Sixty-six (66) mixed breed beef calves weighing approximately 400 lbs and meeting the criteria of acute BRD (fever, dyspnoea, and moderate clinical illness index score) were randomly divided into 4 treatment groups. All groups received ceftiofur at 0.5 mg/lb daily for 3 days. In addition, three groups received a single dose of either flunixin meglumine (2.2 mg/kg IV), ketoprofen (3 mg/kg) IV or carprofen (1.4 mg/kg) SC. All animals were monitored throughout the trial and for 1 to 2 days post-treatment for clinical signs, fever, mortality and adverse reactions. At the termination of the study, all animals were sacrificed and the lung lesions were described and scored for percent consolidation.

Results showed that treatment with any of the three NSAID's reduced fever statistically significantly more rapidly than the antibiotic alone. All groups showed improvement in clinical illness scores and dyspnoea throughout the study. There were no statistical differences between any of the treatment groups.

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[12] "*Detection of Flunixin Meglumine and Phenylbutazone Residues in Raw Milk by ELISA Screening*" http://www.cfsan.fda.gov/~frf/forum02/a194s7.htm

[13] http://oacu.od.nih.gov/ARAC/tablesbyspecies.pdf