

-Flunixin (Banamine®)- Livestock

Executive Summary

Flunixin is a synthetic drug more commonly made into flunixin meglumine, which is the primary component of Banamine® (the injectable flunixin meglumine solution). It has been FDA approved and used in horses for many years to help cope with inflammation, pyrexia, and colic. Administered intravenously and intramuscularly, flunixin is quickly broken down internally and cleared from the bloodstream in urine.

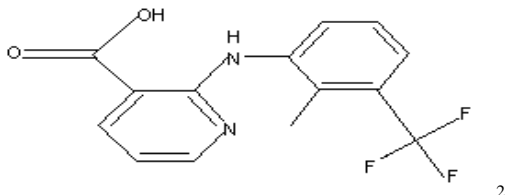
Organic farmers have petitioned the use of flunixin for cattle in order to treat inflammation and pyrexia. They would like to treat livestock specifically endangered by Bovine Respiratory Disorder with flunixin meglumine in order to help the animal deal with pain and other symptoms. If all precautions are followed and the drug is administered appropriately, there will be no harm done to humans who consume the meats from these animals—and the livestock are able to cope with the disorder and actually heal from it, quickly recovering, and granting the farmer economic satisfaction.

Summary of TAP Reviewer's Analyses¹

| <i>Synthetic/ Nonsynthetic</i> | <i>Allow without restrictions?</i> | <i>Allow only with restrictions? (See Reviewers' comments for restrictions)</i> |
|------------------------------------|------------------------------------|---|
| Synthetic (3) Nonsynthetic (0) | Yes (0) No (3) | Yes (0) No (3) |

Identification

Chemical names: Flunixin, C₁₄H₁₁F₃N₂O₂



Other Names: Flunixin; Flunixin [USAN:BAN:INN]; Flunixin [USAN]; 2-(alpha(sup 3) alpha (sup 3), alpha (sup 3)-Trifluoro-2,3-xylidino)nicotinic acid; Flunixine [INN-French]; Flunixino [INN-Spanish];

¹ This Technical Advisory Panel (TAP) review is based on the information available as of the date of this review. This review addresses the requirements of the Organic Foods Production Act to the best of the investigator's ability, and has been reviewed by experts on the TAP. The substance is evaluated against the criteria found in section 2119(M) of the OFPA [7 USC 6517(m)]. The information and advice presented to the NOSB is based on the technical evaluation against that criteria, and does not incorporate commercial availability, socio-economic impact, or other factors that the NOSB and the USDA may want to consider in making decisions.

² "Flunixin [38677-85-9]" ChemFinder.Com Search Result Page
<http://chemfinder.cambridgesoft.com/result.asp>

Flunixinum [INN-Latin]; Sch 14714; 2-(2'-Methyl-3'-trifluoromethylanilino)nicotinic acid; 3-Pyridinecarboxylic acid, 2-((2-methyl-3-(trifluoromethyl)phenyl)amino)-

CAS Number: 38677-85-9³

Other Numbers: ACX X1017251-9⁴

ANADA Number: 200-142 (flunixin meglumine solution)

Characterization

Composition: Flunixin, is most commonly found for uses in organic farming in its compounded state called *Flunixin Meglumine*, ($C_{14}H_{11}F_3N_2O_2C_7H_{17}NO_3$)⁵. Flunixin Meglumine is a potent, non-narcotic, non-steroidal analgesic agent with anti-inflammatory and antipyretic activity. It is a potent inhibitor of the enzyme cyclooxygenase and is often classified as a non-steroidal anti-inflammatory drug (NSAID).⁶ It is also important to note that flunixin exists with a counterclockwise hysteresis that pertains greatly to the pharmacokinetics and pharmacodynamics of drugs in general. As a pair of stereoisomers, in particular, enantiomers, flunixin exists in drug form as a racemic (50:50) mixture of the sinister, "S", as well as the rectus, "R" designation, pertaining to the two different non-superimposable mirror images of the two separate molecules.⁷

Properties:

Note: *All italicized statements refer to properties of Flunixin Meglumine*

Appearance: *A white to almost white powder*

Melting Point: *137°C – 140°C*

Molecular Weight: *296.2483; 491.5*

Identification: *Infrared Spectrum: conforms to reference standard*

Ultraviolet Absorption: conforms to reference standard

Stability: *pKa=5.82; weak acid*

pH (0.25% solution): *7.5 - 8.0*

Clarity and Color of Solution: *A freshly prepared 5% w/v solution will be clear*

Specific Rotation: *9 to 12 calculated with reference to the dried substance*

Loss on Drying: *Not more than 0.5%*

Residue on Ignition/Sulphated Ash: *Not more than 0.2%*

Related Substances: *by TLC*

a) individual impurities 0.2%

b) not more than two impurities > 0.1%

c) total impurities 0.5%

Assay: *by titration 99.0-101.0%*

Residual Solvents: *Ethanol-Not more than 0.1%*

Methanol- Not more than 0.1%

Isopropanol- Not more than 0.1%

Ethyl Acetate- Not more than 0.4%.⁸

Compatibility: *High plasma protein binding (99%).⁹*

³ "Flunixin [USAN] RN: 38677-85-9" ChemIDplus.

http://chem.sis.nlm.nih.gov/chemidplus/detail_head.html?DetailIndex=1&DetailCount=1

⁴ "Flunixin [38677-85-9]" ChemFinder.Com Search Result Page

<http://chemfinder.cambridgesoft.com/result.asp>

⁵ "Flunixin Meglumine." <http://www.norbrook.co.uk/PDF/ChemSynth/Flunixin%20Meglumine.pdf>.

⁶ "Banamine. Research Background" <http://63.236.84.42/research/bfmsic.html>

⁷ "Managing Chronic Pain: The NSAIDs" World Small Animal Veterinary Association.

<http://www.vin.com/VINDBPub/SearchPB/Proceedings/Pro5000/>

⁸ Note: all statements italicized were found under the compound "Flunixin Meglumine."

<http://www.norbrook.co.uk/PDF/ChemSynth/Flunixin%20Meglumine.pdf>.

⁹ "Flunixin [USAN] RN: 38677-85-9" ChemIDplus.

http://chem.sis.nlm.nih.gov/chemidplus/detail_head.html?DetailIndex=1&DetailCount=1

How Made:

Aspirin was the first analgesic patented for humans to inhibit the formation of prostaglandins within the body. Thus, the first “painkiller” was born. Since then, there have been many analgesics designed for veterinary medicine in addition to aspirin: phenylbutazone, ketaprofen, carprofen, tolfenamic acid, and amongst these listed, flunixin meglumine.¹⁰ Banamine® is the only patented form of flunixin meglumine that is allowed for use on cattle in the United States.¹¹ Each milliliter of BANAMINE® Injectable Solution contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol; 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

Specific Uses:

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, Banamine®, exists for intravenous or intramuscular use in horses and for intravenous use in beef and non lactating dairy cattle only.¹² Banamine® has been used to rapidly reduce the fever and lung inflammation that typically accompany bovine respiratory disease (BRD). As a result of usage, cattle feel better faster and have fewer lung lesions in comparison to treatment with other remedies.¹³ Additionally, Banamine® has been used to reduce inflammation associated with endotoxemia.¹⁴

Action:

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.¹⁵

Flunixin meglumine is an NSAID and it functions by reducing the production of mediators of the inflammatory process. Specifically, it acts as an anti-inflammatory by inhibiting the effect of prostaglandins. In particular, it inhibits cyclooxygenase (COX), the enzyme responsible for the direct synthesis of prostaglandins.

In the base of the brain, there is a temperature regulating center located in the hypothalamus. With the help of nerve receptors throughout the skin and spinal cord, feedback that drives the body to either conserve heat, produce increased quantities of heat, or increase heat loss is communicated to the hypothalamus. In a normally operating thermal system, the temperature of the body is regulated by these nervous feedback mechanisms. There are, however, interfering substances (called pyrogens) that create instances which lead to the rise of the “set point” of the hypothalamic thermostat. Pyrogens can consist of proteins, products of proteins, and lipopolysaccharide toxins, all secreted by bacteria. These pyrogens are what cause fever during disease conditions in animals and it does not take much to do so because as little as a few nanograms (one billionth) is sufficient enough to cause fever. Whether the affect on temperature regulation

¹⁰ “Banamine. Research Background” <http://63.236.84.42/research/bfmsic.html>

¹¹ “Banamine: Welcome to the Banamine Web Site” <http://63.236.84.42/home.html>

¹² “SPAH Product Information: Banamine.” <http://usa.spah.com/usa/products/labels/label226.cfm>

¹³ “Banamine: Welcome to the Banamine Web Site” <http://63.236.84.42/home.html>

¹⁴ “Banamine: Banamine Snapshot” <http://63.236.84.42/snapshot/aane.html>

¹⁵ “Managing Chronic Pain: The NSAIDs” World Small Animal Veterinary Association.
<http://www.vin.com/VINDBPub/SearchPB/Proceedings/Pro5000/>

in the hypothalamus is direct (through the bacteria themselves) or indirect (through dead white blood cells that release pyrogens after ingesting the foreign substances) is still being debated. Either way, as a result of the new “set-point,” the body is forced to adjust to this new thermostat setting and the result is usually shivering, chills, and vasoconstriction (decrease blood flow). The thermostat is only lowered to its original setting if and when the pyrogen is removed and the body then tries to reduce the temperature by sweating and vasodilation (increase blood flow), resulting in heat loss. Pyrexia, or fever, has some dangers that result from excessively high temperatures in response to pyrogens: body cells are destroyed, particularly nerve cells, which is dangerous because they do not regenerate. Pathologically, death due to hyperpyrexia is caused by localized hemorrhages and degeneration of cells throughout the body.

Within the circulatory system and its blood-borne cells, there is another response that takes place in response to injury—whether physical, chemical, or infectious—inflammation. Inflammation is necessary in order for healing to take place. However, its effect on body tissues and organs may be excessive and cause damage and therefore, there are certain situations in which controlling the onset of inflammation may be beneficial to the individual. Inflammation is actually broken down into two definitive parts: the “histamine dependant” phase, when blood cells migrate into the tissues and release substances such as histamine; the second phase being the release of a host of mediators including kinins, complement, and prostaglandins. These substances are released from damaged blood and tissue cells, which cause further damage and increase the inflammatory response. The inflammatory process continues as long as the noxious agents persist. When the noxious agents are eliminated, local mediators are turned off by dilution, removed via the lymphatics, and rapidly metabolized by enzyme systems.

In the second phase of the inflammation process, the mediator prostaglandin is released. A chain reaction commencing with the release of unsaturated fatty acids from cells results in the desired end products—prostaglandins. The enzyme complex, cyclooxygenase, which is released from the cell membrane, effects the conversion of fatty acids to prostaglandins. These prostaglandins are found everywhere throughout the body and are not just synthesized in response to tissue injury. Not only are they synthesized upon need, but they metabolize very quickly, never staying near where they were synthesized, and not usually reaching the systematic circulation for redistribution. High concentrations of prostaglandins have been directly associated with pain because of its direct action upon nerve endings. However, it is more common that at low concentrations, they dramatically increase sensitivity to pain. Sometimes, the pain threshold is so altered that normally painless stimuli become painful and the effect is long-lasting and cumulative. The production of prostaglandins, with consequent induction of pain, results from the release of digestive enzymes by phagocytes in response to foreign substances. Additionally, prostaglandins are responsible for pain perception within the nervous system as well. They are produced in the nervous system and sensitize it to pain as well, much like its production in the local area of concentration.

Prostaglandins are a contributor to the inflammatory process, acting as a potent mediator—infiltrated by the noxious agents—and causing increased blood flow, chemotaxis (summoning of WBC), and the resulting tissue and organ dysfunction. The inflammatory process induces pyrexia (fever) through infectious agents, toxins, and tissue fluids that enter the circulation. As a result, prostaglandins are produced in the central nervous system (CNS) as well, particularly in the anterior hypothalamus. With Pyrexia, depression and inappetence may occur and prostaglandins are also associated with these signs.

As an NSAID, flunixin meglumine produces an anti-inflammatory effect by inhibiting the production of prostaglandins. In preventing the synthesis of prostaglandins by inhibiting the enzyme cyclooxygenase, NSAIDs function by reducing the production of mediators of the inflammatory process. Additionally, since prostaglandins are known for their induction of pain upon the individual, anti-prostaglandins also act as an analgesic (“pain-killer”).

Recent studies have determined that there are two forms of cyclooxygenase—COX-1 and COX-2—which, respectively, correspond to the “good” effects of prostaglandins, such as gastric acidity and intestinal mucous flow, and “bad” effects of prostaglandin, such as inflammation, pyrexia, and pain. Although a COX-2 directed form of anti-prostaglandin would seem desirable, scientists have yet to demonstrate this laboratory extrapolated theory on humans or animals.

Flunixin meglumine is a potent, non-narcotic, non-steroidal analgesic with anti-inflammatory and antipyretic activity. It is an inhibitor of the enzyme cyclooxygenase and seems to be four times as potent as phenylbutazone and twice as potent as ketoprofen.¹⁶

Combinations:

As previously stated, flunixin is administered in its drug form as Banamine®, which is a product primarily made up of the compound, flunixin meglumine.

Status

Historic Use by Organic Farmers:

Cattle: Pyrexia in cattle is considered dangerous when temperature readings reach about 106-107°F from the normal 101.5°F or if they prolong for an excessive duration of several days. Effective treatment of the infectious agents removes the source of fever-causing toxins and the fever declines rapidly. Flunixin meglumine (an NSAID) is used in the treatment of pyrexia specific to bovines.

Regarding inflammatory diseases in cattle, there are many. One of the most common infections involves the respiratory tract. Colloquially known as bovine respiratory disease (BRD), it is a combination of gram negative bacteria and viral agents usually caused by one of the following bacteria: *Pasteurella haemolytica*, *Pasteurella multocida*, or *Haemophilus somnus*.¹⁷ Clinically, it can range from mild to severe pneumonia. Characterized by sudden onset of fever, depression, lethargy, decreased appetite, and a tendency to be away from herdmates, BRD exists primarily in dairy and beef calves from birth to weaning and is probably most commonly seen post-weaning. Some adults can be hosts for it as well although it is less likely. As a result, inflammatory conditions of the lung are characterized by decreased oxygenation of blood. If there is pleurisy (pleura—covering of the lungs—inflammation), the animal will experience pain with every breath. If this persists, there can be lung damage leading to a decreased lung capacity. As a result, future growth and production will be affected. In conclusion, flunixin meglumine ameliorates some of the clinical signs of bovine respiratory disease and demonstrates efficacy as an antipyretic.¹⁸ Field studies have proven that flunixin meglumine along with antibiotics for bovine respiratory disease can reduce illness scores, fever, lung consolidation, and death loss in calves.¹⁹

Toxemia develops in infected individuals because of bacterial infection and significant tissue damage that occur when white blood cells are destroyed.²⁰ Endotoxemia occurs both as the animal's immune system attacks bacteria and as antibiotics disrupt the ability of bacteria to repair themselves. As a result, the bacteria break up, fall apart and release cell wall parts that contain endotoxins into the body. These endotoxins cause inflammation and tissue damage in the lungs.²¹ Flunixin meglumine (Banamine®) helps control endotoxemia²² which leads to lung lesions, slowing recovery and possibly resulting in life-

¹⁶ "Banamine. Research Background." <http://63.236.84.42/research/bfmic.html>

¹⁷ "Anti-Inflammatory Speeds Recovery in Cattle with Bovine Respiratory Disease." Banamine Usage Reports. http://63.236.84.42/usage_reports/aisric.html

¹⁸ "Banamine. Research Background." <http://63.236.84.42/research/bfmic.html>

¹⁹ "Research Shows Advantages of Using Banamine with Conventional Therapy." Banamine Usage Reports. http://63.236.84.42/usage_reports/rsaoub.html

²⁰ "Practitioners See Many Potential Uses for Newly Approved Anti-Inflammatory Agent for Cattle." Banamine Usage Reports. http://63.236.84.42/usage_reports/psmpu.html

²¹ "Like a Grenade in an Ammunitions Depot" Banamine Usage Reports. http://63.236.84.42/usage_reports/lagiaad.html

²² "Banamine: Banamine Snapshot" <http://63.236.84.42/snapshot/aane.html>

threatening illness.²³ Contrary to popular belief, flunixin meglumine is not licensed for use in cattle as a pre-operative analgesic.²⁴

Horses: Flunixin is used in horses to treat colic. Abdominal pain (colic) is caused by distention of the bowel wall, stretching of the mesentery, inflammation of the intestinal wall or peritoneum, or ischemia and spasm of the intestinal musculature. A horse typically shows symptoms of colic by pawing, sweating, getting up and down, stretching out, crouching, rolling, kicking at abdomen, and turning towards flank. Flunixin meglumine is administered in horses with mild and moderate colic in order for pain control and to prevent gastric rupture.²⁵ It is also used for alleviating pain and inflammation due to musculoskeletal disorders and intestinal pain associated with colic.²⁶

A rectal tear is signaled when there is a sudden loss of resistance during palpation and when copious amount of fresh blood is present on the rectal sleeve. Flunixin meglumine can be used as an analgesic along with antibiotics and a laxative diet when treating grade I and II rectal tears in horses.²⁷

Goats: It is used in respiratory infections to combat attendant inflammation of the lungs. Flunixin meglumine relieves coughing and dyspnea and areas of consolidation in the lungs.²⁸

OFPA, USDA Final Rule:

OFPA states in Sec. 6509(d):

(d) **Health Care.**

(1) **Prohibited Practices.** For a farm to be certified under this chapter as an organic farm with respect to the livestock produced by such farm, producers on such farm shall not

- (A) use subtherapeutic doses of antibiotics;
- (B) use synthetic internal paratitcides on a routine basis; or
- (C) administer medication, other than vaccinations, in the absence of illness.²⁹

Flunixin is found as flunixin meglumine in the drug Banamine® and it is often used by veterinarians to treat inflammation and pain. As stated above in the final rule, there seems to be room for formidable debate as long as the dosage requirements are met for certain drugs.

Policies from the FDA:

Note: The following law pertains to the legal dosage of flunixin meglumine allowed in animals. Relevant information specifically referring to cattle and livestock has been highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

²³ "Like a Grenade in an Ammunitions Depot" Banamine Usage Reports.

http://63.236.84.42/usage_reports/lagiaad.html

²⁴ Parks, Dr. Andrew. "Bovine Abdominal Surgery" LAMS 5350.

<http://lam.vet.uga.edu/LAM/LM000056.HTML>

²⁵ Moore, Dr. James N. "Equine Digestive System" LAMS 5350.

<http://lam.vet.uga.edu/LAM/LM000021.HTM>

²⁶ "Like a Grenade in an Ammunitions Depot" Banamine Usage Reports.

http://63.236.84.42/usage_reports/lagiaad.html

²⁷ Hardy, Joanne. "Emergency Procedures in Equine Trauma and Critical Care" http://www.vet.ohio-state.edu/docs/vm700_16/procedures.doc

²⁸ Fias Co Farm. "Goat Medications." <http://fiascofarm.com/goats/medications.htm>

²⁹ 6509 Animal Production Practices and Materials. Federal Organic Food Production Act of 1990. <http://www.ams.usda.gov/nop/orgact/htm>

PART 522--IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS--
Table of Contents

Sec. 522.970 Flunixin meglumine solution.

(a) Specifications. The drug contains 50 milligrams of flunixin per milliliter of aqueous solution.

(b) Sponsors. See 000061 in Sec. 510.600(c) of this chapter for use as in paragraph (d) of this section. See 000856 and 059130 for use as in paragraph (d)(1) of this section only.

(c) Related tolerances. See Sec. 556.286 of this chapter.

(d) Conditions of use--

(1) Horses--(i) Amount. 0.5 milligram of flunixin per pound of body weight (1 milliliter per 100 pounds) per day.

(ii) Indications for use. For alleviation of inflammation and pain associated with musculoskeletal disorders, and alleviation of visceral pain associated with colic.

(iii) Limitations. For musculoskeletal disorders, administer intravenously or intramuscularly for up to 5 days. For colic, administer a single dose intravenously--treatment may be repeated when signs of colic recur. Caution: The effect of this drug on pregnancy has not been determined. Not for use in horses intended for food. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

(2) Beef cattle and nonlactating dairy cattle--(i) Amount. 1.1 to 2.2 milligrams per kilogram of body weight (0.5 to 1 milligram per pound, 1 to 2 milliliters per 100 pounds), once a day as a single dose or divided into 2 doses administered at 12-hour intervals for up to 3 days.

(ii) Indications for use. For control of pyrexia associated with bovine respiratory disease and endotoxemia. Also indicated for control of inflammation in endotoxemia.

(iii) Limitations. Do not slaughter for food use within 4 days of last treatment. Not for use in lactating or dry dairy cows. A withdrawal period has not been established for use in preruminating calves. Do not use in calves to be processed for veal. Do not use in bulls intended for breeding as reproductive effects in this class of cattle have not been studied. Federal law restricts this drug to use by or on the order of a licensed veterinarian.

[42 FR 39103, Aug. 2, 1977, as amended at 52 FR 7832, Mar. 13, 1987; 60 FR 54942, Oct. 27, 1995; 62 FR 22888, Apr. 28, 1997; 63 FR 38749, July 20, 1998]

Note: The following law pertains to the related tolerances for residues associated with flunixin meglumine.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 556--TOLERANCES FOR RESIDUES OF NEW ANIMAL DRUGS IN FOOD--Table of Contents

Subpart B--Specific Tolerances for Residues of New Animal Drugs

Sec. 556.286 Flunixin meglumine.

(a) Acceptable daily intake (ADI). The ADI for total residues of flunixin is 0.72 micrograms per kilogram of body weight per day.

(b) Tolerances. For residues of parent flunixin free acid of 0.125 part per million (ppm) in cattle liver (target tissue) and 0.025 ppm in cattle muscle are established.

[63 FR 38750, July 20, 1998]

Note: The following law indicates the legal dosage allowed for the granules form of flunixin meglumine. Relevant information has been highlighted and italicized.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 520--ORAL DOSAGE FORM NEW ANIMAL DRUGS--Table of Contents

Sec. 520.970a Flunixin meglumine granules.

(a) Specifications. Each 10-gram packet contains flunixin meglumine equivalent to 250 milligrams of flunixin.

(b) Sponsor. No. 000061 in Sec. 510.600(c) of this chapter.

(c) Conditions of use--(1) Amount. 0.5 milligram of flunixin per pound of body weight (one packet per 500 pounds) per day.

(2) Indications for use. For alleviation of inflammation and pain associated with musculoskeletal disorders in the horse.

(3) Limitations. Administer daily dose for up to 5 days by sprinkling on small amount of feed. ***The effect of this drug on pregnancy has not been determined. Not for use in horses intended for food. Federal law restricts this drug to use by or on the order of a licensed veterinarian.***

[44 FR 36381, June 22, 1979. Redesignated at 50 FR 38114, Sept. 20, 1985, and amended at 52 FR 7832, Mar. 13, 1987]

Note: The following law addresses the paste form of flunixin meglumine. Relevant information has been highlighted.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 520--ORAL DOSAGE FORM NEW ANIMAL DRUGS--Table of Contents

Sec. 520.970b Flunixin meglumine paste.

(a) Specifications. Each 30-gram syringe contains flunixin meglumine equivalent to 1,500 milligrams of flunixin.

(b) Sponsor. No. 000061 in Sec. 510.600(c) of this chapter.

(c) Conditions of use. Horses--(1) Amount. 0.5 milligram of flunixin per pound of body weight daily.

(2) Indications for use. For alleviation of inflammation and pain associated with musculoskeletal disorders.

(3) Limitations. For oral use only. Treatment should not exceed 5 consecutive days. ***The effect of this drug on pregnancy has not been determined. Not for use in horses intended for food. Federal law restricts this drug to use by or on the order of a licensed veterinarian.***

[50 FR 38114, Sept. 20, 1985, as amended at 52 FR 7832, Mar. 13, 1987]³⁰

Note: The following document is a recent (April 2002) approval by the FDA regarding flunixin meglumine use on livestock.

This supplemental application provides for use of flunixin meglumine solution by intravenous injection for control of fever and inflammation in beef cattle and nonlactating dairy cattle (new species).

Trade Name: Flunixin Meglumine Injection

Ingredients: Flunixin Meglumine

Sponsor: Phoenix Scientific, Inc.

Approval Date: November 1, 2001

Status: Prescription only

Route: Intravenous, intramuscular (horses only)

Species: Horses, cattle (new)

Drug Form: Liquid (solution)

Concentration: 50 milligrams per milliliter

Indications: For use in cattle for the following: control of pyrexia associated with bovine respiratory disease and endotoxemia, and control of inflammation in endotoxemia.

Tolerance: 21 CFR 556.286 Flunixin meglumine: Tolerances are established for residues of parent flunixin free acid of 0.125 part per million (ppm) in cattle liver (target tissue) and 0.025 ppm in cattle muscle.

Withdrawal: 4 days

³⁰ All above laws regarding epinephrine and its legal use were directly copied and pasted from the government archives found on the web under relevant sections that pertained to this research. No alterations were made except certain significant information within the original text was highlighted for convenience purposes as previously noted. <http://www.accessdata.fda.gov/scripts>

21CFR 522.970³¹

Regulatory: EPA/NIEHS/Other Sources

EPA: In a report on PPCP (Pharmaceuticals and Personal Care Products) that are found in the environment, particularly in the water, flunixin was *not* among the other NSAIDs (i.e. aspirin, ibuprofen, etc) that had residues left in the waters. However, it should be noted that the table only showed a handful of materials and there was a disclaimer written on the document stating that not all materials were even tested.³²

NTP, IARC: not listed as a known carcinogen³³

NOSB: Flunixin material is scheduled to be petitioned in September 2002

Category: Livestock

Petitioned Use of Material: Pain Reliever, Anti-Inflammatory

OSHA: none

NIOSH: The following attachment was found in the archives of the NIOSH website and it pertains to a list of medications under review with regards to employees and their exposure to Cadmium. There is no real relation to livestock since there has not been any official information regarding the affect of NSAIDs mixed with cadmium exposure.

Appendix A - Attachment - 2: List of Medications

A list of the more common medications that a physician, and the employee, may wish to review is likely to include some of the following: (1) anticonvulsants: paramethadione, phenytoin, trimethadone; (2) antihypertensive drugs: captopril, methyldopa; (3) antimicrobials: aminoglycosides, amphotericin B, cephalosporins, ethambutol; (4) antineoplastic agents: cisplatin, methotrexate, mitomycin-C, nitrosoureas, radiation; (5) sulfonamide diuretics: acetazolamide, chlorthalidone, furosemide, thiazides; (6) halogenated alkanes, hydrocarbons, and solvents that may occur in some settings: carbon tetrachloride, ethylene glycol, toluene; iodinated radiographic contrast media; **nonsteroidal anti-inflammatory drugs**; and, (7) other miscellaneous compounds: acetaminophen, allopurinol, amphetamines, azathioprine, cimetidine, cyclosporine, lithium, methoxyflurane, methysergide, D-penicillamine, phenacetin, phenindione. A list of drugs associated with acute interstitial nephritis includes: (1) antimicrobial drugs: cephalosporins, chloramphenicol, colistin, erythromycin, ethambutol, isoniazid, paraaminosalicylic acid, penicillins, polymyxin B, rifampin, sulfonamides, tetracyclines, and vancomycin; (2) other miscellaneous drugs: allopurinol, antipyrine, azathioprine, captopril, cimetidine, clofibrate, methyldopa, phenindione, phenylpropanolamine, phenytoin, probenecid, sulfapyrazone, sulfonamid diuretics, triamterene; and, (3) metals: bismuth, gold.

This list has been derived from commonly available medical textbooks (e.g., Ex. 14-18). The list has been included merely to facilitate the physician's, employer's, and employee's understanding. The list does not represent an official OSHA opinion or policy regarding the use of these medications for particular employees. The use of such medications should be under physician discretion.³⁴

³¹ Actions Taken by FDA Center for Veterinary Medicine: *Supplementary Approvals ANADA No. 200-124*
<http://www.fda.gov/cvm/greenbook/0402supp.htm>

³² Daughton, Christian G. "Pharmaceuticals and Personal Care Products in the Environment: Overarching Issues and Overview" <http://www.epa.gov/esd/chemistry/pharma/book-summary.htm>

³³ Chemical Hygiene Plan, Appendix C: *Carcinogens*.

³⁴ Regulations (Standards - 29 CFR) *Substance Safety Data Sheet - Cadmium - 1910.1027 App*
http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10036&p_search_type=STANDTEXTPOLICY&p_search_str=anti-inflammatory&p_text_version=FALSE#ctx1

ACGIH: none

NIEHS: In a research conducted on Prostaglandin 1 and 2, the following information was listed:

“NSAIDs (nonsteroidal antiinflammatory drugs), whose mechanism of action is believed to be through inhibition of the cyclooxygenases, have been shown to inhibit colon cancer in addition to their antiinflammatory effects (and their ulcerative side effects).”³⁵

In a separate article of interest, NIEHS claims to be conducting research on the effects of NSAIDs in the body and whether the changes that the drugs create could lead to potential damage later on:

“Because one of the unanswered questions is whether NSAIDs or other types of inhibitors are effective preventive agents because they are altering pathways other than their intended targets, studies are underway using gene expression approaches, principally SAGE (Serial Analysis of Gene Expression) to determine what these changes are and whether there are common changes that could function as biomarkers.”³⁶

Flunixin is a major component of some analgesics, which are taken in response to pain and inflammation. It has been reported that analgesics and other NSAIDs are the most commonly taken drugs. If this is such, it seems as though there are no real dangers to the drug besides some minor side effects that surface along with overdose and general abuse.

Status Among U.S. Certifiers

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

- non-steroidal anti-inflammatory (i.e. Banamine®)
- antihistamines (e.g. epinephrine, adrenaline)
- anesthetics”³⁷

Pennsylvania/Minnesota/Oregon: Go along with the OMRI status. Flunixin is a synthetic drug currently under consideration according to the OMRI. As long as dosage and use is regulated and observed, Banamine® will be great help to veterinarians who deal with organic livestock.³⁸

International

IFOAM Basic Standards:

5.7. Veterinary Medicine

General Principles

Management practices should be directed to the well being of animals, achieving maximum resistance against disease and preventing infections.

Sick and injured animals must be given prompt and adequate treatment.

Recommendations

Natural medicines and methods, including homeopathy, ayurvedic medicine and acupuncture, should be emphasised.

When illness does occur the aim should be to find the cause and prevent future outbreaks by changing management practices.

Where appropriate the certification bodies should set conditions based on the farm’s veterinary records to minimise the use of medicines.

³⁵ Chapter X - Risk Assessment Research (Molecular Biology of Gene Expression of Chemical Metabolizing Enzyme Systems): Mouse Model: *Targeted Gene Knockout of Prostaglandin Synthase 1 and 2*. http://ntp-server.niehs.nih.gov/htdocs/AP/10_Molec_Biol.html

³⁶ Mechanisms of Disease Prevention Research Core <http://www.niehs.nih.gov/centers/res-core/uts-res5.htm>

³⁷ *VOF Organic Meat & Egg Production – NOFA Vermont* http://www.nofavt.org/sht02_stds7.cfm

³⁸ Karreman, Hubert J. *PCO POSITION PAPER ON THE USE OF FLUNIXIN, PHENYL BUTAZONE, FUROSEMIDE AND OXYTOCIN IN CERTIFIED ORGANIC LIVESTOCK.*

The certification body/ standardising organisation should make a list of medicines and withholding periods.

Standards

5.7.1.

The well-being of the animals is the primary consideration in the choice of illness treatment. The use of conventional veterinary medicines is allowed when no other justifiable alternative is available.

5.7.2.

Where conventional veterinary medicines are used, the withholding period shall be at least double the legal period.³⁹

European Union (EU): Flunixin is a drug that has been approved for use in swine in Europe (MRL = 50: g/kg in muscle). This drug is not included in the Drug Residue plan in Belgium so there is no guarantee that there would be no detectable residues found in pork.⁴⁰

Canadian General Standards: Canadian General Standards: Canada possesses 3 standards of beef—natural beef, certified organic beef, and certified hormone-free beef. Natural beef consists of beef that has not been treated with antibiotics or hormones.⁴¹

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.*

Researchers found that when Banamine® was combined along with antibiotic treatment, the results were very promising: the calves showed a faster, steeper reduction in mean rectal temperatures, significantly fewer fevers, higher feed intake, as well as non-apparent gross consolidation from fibrinous pneumonia.⁴²

Although there are no listed avoidable combinations for flunixin in particular, there have been studies done on other related NSAIDs such as aspirin which may be relevant to flunixin as well since they have the same pharmacokinetic makeup:

“Aspirin can be taken safely with many other medications. There are some drugs, however, such as certain ones taken for gout and diabetes, that should not be taken with aspirin. It is very important to tell your doctor all the drugs you are taking for any condition. This includes any medications bought without a prescription and those prescribed by another doctor.”⁴³

The following should not be taken along with NSAIDs:

- aspirin or another salicylate (form of aspirin)

³⁹ *IFOAM Basic Standards 2000* <http://www.ifoam.org/standard/basics.html#10>

⁴⁰ *Audit Report for Belgium: May 16 through May 26, 2000.*

<http://www.fsis.usda.gov/OFO/TSC/ForeignCtryAudRepts/Documents/Belgium.PDF>

⁴¹ *Canada Beef Export Federation February 2001* http://www.agric.gov.ab.ca/agdex/400/420_830-3.pdf

⁴² *Banamine: Technical Data* <http://63.236.84.42/technical/eofmaot.html>

⁴³ *Medications for Arthritis: Aspirin and Related Drugs (NSAIDs)*

<http://www.orthop.washington.edu/arthritis/medications/nsaids/03>

- an over-the-counter cough, cold, allergy, or pain medicine that contains aspirin, ibuprofen, naproxen, or ketoprofen;
- a diuretic (water pill)
- an angiotensin-converting-enzyme (ACE) inhibitor for blood pressure
- a beta-blocker for heart problems
- a calcium channel blocker for heart problems
- an anticoagulant (blood thinner) such as warfarin
- a steroid such as prednisone (corticosteroid injection for pain and inflammation)
- an oral diabetes medicine
- lithium for psychological problems

Avoid prolonged exposure to sunlight. NSAIDs may increase the sensitivity of your skin to sunlight. Use a sunscreen and wear protective clothing when exposure to the sun is unavoidable.⁴⁴

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.*

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.⁴⁵ 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.

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

As aforementioned, there are no dangers about flunixin, flunixin meglumine, or Banamine® listed. But as a general precaution, 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.⁴⁶

“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

⁴⁴ *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>

⁴⁵ *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>

⁴⁶ “Banamine. Research Background” <http://63.236.84.42/research/bfmsic.html>

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 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® Corporation's 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.”⁴⁷

Additionally, taking high doses of nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin, ibuprofen (Advil, Motrin, etc.), and naproxen sodium (Aleve) for long periods of time put you at risk for stomach pain, bleeding from gastritis or ulcers, and even kidney failure. And while acetaminophen does not cause stomach upset, research suggests that taking just one pill daily for a year doubles the risk of kidney disease. It has also been found that the risk of liver damage is higher in people who drink alcohol and don't eat before taking acetaminophen.⁴⁸

Generally, NSAIDs should not be used by people who:

- have an allergy to aspirin or any other NSAIDs,
- have an ulcer or bleeding in the stomach,
- drink more than three alcoholic beverages a day,
- have liver or kidney disease,
- have a coagulation (bleeding) disorder,
- have congestive heart failure,
- have fluid retention,
- have heart disease, or
- have high blood pressure.

With regards to pregnant women, the following suggestions are made regarding NSAID use:

Some NSAIDs are in the USA Federal Drug Administration pregnancy category B. This means that they are not likely to harm an unborn baby. Other NSAIDs are in the FDA pregnancy category C. This means that it is not known whether they will harm an unborn baby. *No NSAIDs may be taken late in pregnancy (the third trimester) because they can affect the baby's heart.* Do not take an NSAID without first talking to your doctor if you are pregnant.

Some NSAIDs pass into breast milk and may affect a nursing infant. Do not take an NSAID without first talking to doctor if breast-feeding a baby.

If over the age of 65 years, the patient may be more likely to experience side effects from NSAID therapy. The doctor may advise using a lower dose or have special monitoring during treatment.

Only the following NSAIDs (of certain dosages as directed by a doctor or pharmacist) are approved for use by children less than 18 years old [in the USA]:

- mefenamic acid (Ponstan) and indomethacin (Arthrexin, Rheumacin, Indocid) - 15 years old;
- naproxen (Naprosyn Synflex, Noflam, Naxen) - 2 years old;

⁴⁷ “*Detection of Flunixin Meglumine and Phenylbutazone Residues in Raw Milk by ELISA Screening*”
<http://www.cfsan.fda.gov/~frf/forum02/a194s7.htm>

⁴⁸ *Safety Check: Over-the-Counter Medications.* <http://www.thehealthpages.com/articles/ar-otcmd.html>

- ibuprofen (Panafen, Brufen) - 6 months old and older.⁴⁹
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.*

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.⁵⁰

With regards to horses, Banamine® comes with very specific guidelines for administration that should be followed:

Trade Name: Flunixin Meglumine Solution

Established Name: Flunixin Meglumine

Dosage Form: Flunixin meglumine is a sterile solution

How Supplied: Flunixin meglumine is supplied in 50 mL and 100 mL multi-dose vials.

How Dispensed: Prescription (Rx)

Amount of Active Ingredients: Each mL contains 50 mg flunixin base

Route of Administration: Intravenous or intramuscular injection

Species: Equine

Labeled Dosage: The recommended dose is 0.5 mg per pound (1 mL/100 lbs.) of body weight once daily for five days.

Indications for Use: “Tradename” (flunixin meglumine) solution is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in horses. It is also recommended for the alleviation of visceral pain associated with colic in horses.

Pioneer Product: Banamine® (flunixin meglumine), manufactured by Schering-Plough Corporation. (NADA 101-479).

Human Safety: Regarding consumption of drug residues in food, human safety data were not required for approval of this ANADA. This drug is labeled for use in horses not intended for food.

Date of Approval: September 25, 1995⁵¹

Studies were conducted in calves to check for acute toxicity of flunixin meglumine and the following was found:

Calves (2 male and 2 female) were administered four intravenous injections of flunixin meglumine in sequential doses of 6.6, 13.2, 26.4 and 52.8 mg/kg (25 times the recommended dose) every other day on a rising dose basis. Results were:

- Seizures — were observed in one calf at 26.4 mg/kg and all four calves at 52.8 mg/kg.
- Mortality — one calf died following the 52.8 mg/kg dose.
- Urinalysis — hematuria and proteinuria were noted after all doses.
- Fecal blood — frank and/or occult blood was observed after the 13.2, 26.4 and 52.8 mg/kg doses.

⁴⁹ *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>

⁵⁰ <http://oacu.od.nih.gov/ARAC/tablesbyspecies.pdf>

⁵¹ NADA 200-142 <http://www.fda.gov/cvm/efoi/section3/200142.html>

- Hematology/Serum Chemistry — slightly increased platelet numbers were observed.
- Gross and Histopathology — no treatment related changes; only nonspecific congestion or hemorrhages were noted in multiple organs of the one animal that died (52.8 mg/kg dose).

In conclusion, flunixin-related changes included blood in the urine and feces following the 26.4 and 52.8 mg/kg doses and seizures and one mortality after the 52.8 mg/kg dose. In the three remaining animals, all parameters returned to normal during the 14-day post-dose observation period except for one animal positive for fecal occult blood and another positive for urine blood at 14 days.⁵²

The drug (Banamine®) was also tested for reproduction safety in livestock and the following observations were made:

The first study was a 12-month reproductive study in which six intravenous injections of flunixin at 3X (6.6 mg/kg) the recommended high end of the dose range were administered to pregnant cattle during selected time points of each trimester of pregnancy. Healthy cows were observed for estrus and bred artificially with frozen semen from the same bull. Twenty four pregnant females were divided into groups of 12 each, treated and control. The treated group received two IV injections of flunixin at approximately 90 days, 150 days and 265 days of pregnancy. Offspring were weighed at birth and 30 days of age and observed for any abnormalities.

In conclusion, no adverse effects in the cows or calves were attributed to intravenous injections of flunixin meglumine given at 3X the recommended dose two times during each trimester of pregnancy.

A second study involved treatment of animals prior to breeding, 12/13 days, 36/37 days, 112/113 days, 210/211 days and 265/266 days post breeding. At each time point, animals received 6.6 mg/kg IV on two consecutive days. All animals were allowed to calve naturally and calves were observed at birth and at 30 days.

In conclusion, no adverse effects in the cows or calves were attributed to flunixin intravenous injections administered to the cows at 6.6 mg/kg for 2 days at 6 time points during the reproductive cycle.⁵³

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

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.

Mean Rectal Temperature (°C)

⁵² "Banamine. Research Background." <http://63.236.84.42/research/bfmic.html>

⁵³ "Banamine. Research Background." <http://63.236.84.42/research/bfmic.html>

| Time | Ceftiofur | Ceftiofur + Carprofen | Ceftiofur + Ketoprofen | Ceftiofur + flunixin |
|------|-----------|--------------------------|---------------------------|-------------------------|
| 0 | 40.5 | 40.5 | 40.6 | 40.5 |
| 2 | 40.3 | 39.7* | 39.1** | 39.1** |
| 4 | 39.7 | 39.3* | 38.8** | 38.9** |
| 6 | 39.5 | 39.1* | 38.9* | 38.9* |
| 12 | 39.1 | 38.9* | 38.6* | 38.6* |
| 24 | 38.8 | 38.5* | 38.5* | 38.5* |
| 48 | 38.7 | 38.7 | 38.7 | 38.7 |
| 72 | 38.8 | 38.6 | 38.7 | 38.9 |

* Statistically significantly different from ceftiofur, p<0.05

** Statistically significantly different from c+ceftiofur, p<0.05

At the termination of the trial, all animals were humanely sacrificed and the lung lesions scored. The one animal that died during the trial was similarly scored. The use of flunixin meglumine in combination with ceftiofur resulted in a statistically significant (p=0.0033) reduction of lung consolidation, which was not attained with either carprofen or ketoprofen.

Median Percent Lung Consolidation

| Treatment | Median % | Number Animals |
|---------------------------|----------|----------------|
| Ceftiofur | 15.3 | 17 |
| Ceftiofur + Carprofen | 5.5 | 16 |
| Ceftiofur + Ketoprofen | 6.3 | 16 |
| Ceftiofur + flunixin | 1.7* | 17 |

*Statistically significantly different from ceftiofur, p<0.05

*These clinical studies demonstrated the anti-inflammatory and antipyretic activity of flunixin meglumine in cattle with bovine respiratory disease.*⁵⁴

Phenylbutazone, commonly known as “bute” is also very commonly used for pain and inflammation in horses because it is effective and inexpensive. This drug, however, remains in the horse’s bloodstream for a long time after each dose, so it is the most common NSAID to cause toxicity. Bute should be given at the lowest possible effective dose and on a once a day basis. For long term use, it’s best to give a low dose every other day. Bute is available in paste and tablets for oral administration and as an injectable product for intravenous administration. If given outside the vein, bute is extremely irritating to muscle tissues. Banamine® is more expensive than bute so it is used to treat colic pain for short term lengths. Unlike bute, flunixin meglumine does not stay in the horse’s bloodstream for a long time and it is less likely to cause toxicity. High doses of Banamine® can still cause kidney and digestive tract toxicity.

⁵⁴ “Banamine. Resaerch Background.” <http://63.236.84.42/research/bfmic.html>

Dipyron is an old drug that is very good at reducing fever, but it does not have a particularly powerful anti-inflammatory or analgesic component like flunixin meglumine. This product is also labeled to be administered intravenously, subcutaneously, or intramuscularly. However, when given intramuscularly, it is extremely irritating to the muscle tissues of the horse.⁵⁵

7. *Its compatibility with a system of sustainable agriculture.*

Flunixin has not been proven to be a hazardous drug. Like other drugs, it should be handled with respect to certain precautions. By using it responsibly, adhering to the given dosages, waiting the allotted legal withdrawal times, and following all instructions with respect to storage, there is no reason why flunixin or any form of it (flunixin meglumine) should cause any direct harm. This, then, is a case of responsibility on the farmer's part.

Since flunixin is only administered with prescription and by a certified veterinarian, the chances of harmful drug misuse can also be regulated. Flunixin meglumine has proven to be a drug that is quickly broken down and removed from the animal's bloodstream through urine and therefore, by waiting the adequate withdrawal time prior to slaughter, there is no real threat posed to humans. Flunixin is basically similar to aspirin in humans (except about 100 times more potent) and just like aspirin, if it is overdosed, there will be effects in the animal's gastrointestinal tract and potential ulceration. But once again, these are all precautionary efforts that are the responsibility of the person administering the drug.

As a synthetic material, flunixin is under consideration by OFPA provided that it is used according to all the regulations and meets all FDA requirements. Being an analgesic and an anti-inflammatory, flunixin is used to care for the animals themselves, relieving them from pain and treating livestock affected with Bovine Respiratory Disorder (BRD) and pyrexia (fever). If used responsibly, there should be no harm done to the system of sustainable agriculture.

TAP Reviewer Discussion

Reviewer #1: [Ph.D., Professor, Department of Food Science, Southeast U.S.]

Comments on Database

The following information needs to be added to the database:

According to 205.603 "Synthetic substances allowed for use in organic livestock production", aspirin is approved for health care use to reduce inflammation. The database does not provide information as to how Flunixin functions differently from aspirin or other similar drugs already approved in the list and why it is needed since Flunixin is also an analgesic like aspirin. The potential side effects of residual Flunixin in livestock to human are not provided.

OFPA Criteria Evaluation

(1) *The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems;*

I agree with the criteria evaluation.

(2) *The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment;*

The potential side effects should be addressed.

(3) *the probability of environmental contamination during manufacture, use, misuse or disposal of such substance;*

The potential environmental contamination during manufacturing is not mentioned.

⁵⁵ "When Good Drugs Do Bad Things" <http://www.agric.gov.ab.ca/livestock/horses/hbo9904.html>

(4) *the effect of the substance on human health;*

The withdraw time of 4 days may not be sufficient and more data should be provided.

(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;*

The section only discusses the general effect of NSAID on human. No specific effect of flunixin on human is provided.

(6) *the alternatives to using the substance in terms of practices or other available materials; and*

I agree with the criteria evaluation.

(7) *its compatibility with a system of sustainable agriculture.*

I agree with the criteria evaluation.

Reviewer 1 Conclusion

Flunixin is a synthetic drug.

Flunixin is classified as a non-steroidal anti-inflammatory drug and a potent inhibitor of the enzyme cyclooxygenase. Similar to aspirin, flunixin is an analgesic agent by inhibiting the synthesis of prostaglandin. Flunixin is a very potent inhibitor of cyclooxygenase (COX), therefore the synthesis of prostaglandin will be inhibited. Recently, COX-2 inhibitor has been approved for treating arthritis in human, suggesting the potential adverse effects of inhibiting COX-1. It is not clear if the use of flunixin would have harmful side effects to livestock beside its anti-inflammatory action.

Flunixin is prohibited for use in horse intended for food (Title 21 - Food and Drugs, sec. 520.970a), therefore it poses potential safety concerns to other livestock intended for human consumption.

Finally, if aspirin can perform similar function as flunixin but just slower, it is safer to use aspirin.

Reviewer 1 Recommendation Advised to the NOSB

The substance is Synthetic

For Livestock, the substance should be Not Added to the National List.

Reviewer #2: [Ph.D, Biochemistry and Molecular Biology, West U.S.]

Observations/OFPA Criteria

Comments on Database

The information provided on the pharmacological action, indications, general side effects, and the status and certification of the use of flunixin in livestock is adequate and fairly accurate. However, some important data, such as tissue concentration of flunixin after conventional doses of the drug, toxicity profile of the drug, particularly hypersensitivity reaction, in humans, are lacking. Also, many of the referenced websites contain errors in their addresses and are not accessible (for example, ref. #7, 9, 16, 18 & 42). A lot of information on flunixin is derived from the manufacturer's website, which raises questions on conflicts of interest and objectivity.

OFPA Criteria Evaluation

(1) the potential of such substances for detrimental chemical interactions with other materials used in organic farming systems

The benefit of combining flunixin with antibiotics in treating certain infections appears to be well established. However, little information is provided on the detrimental potential of flunixin through chemical interactions with other materials used in organic farming systems. This could either support that flunixin is safe or insufficient studies being done on drug interactions of flunixin. Most of the information pertains to aspirin. Both aspirin and flunixin belong to a class of drugs called NSAID and therefore share some common characteristics, such as adverse interactions with other NSAIDs, alcohol, and anticoagulants. However, aspirin and flunixin are chemically distinct, and significant differences in activities and interactions are likely to exist. Considering that flunixin has a high plasma protein binding (99%; ref. #9), it is anticipated that flunixin will potentially interact with many other substances, particularly those that compete with flunixin for plasma protein binding. The extent and severity of the interaction cannot be predicted in the absence of thorough studies.

(2) the toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment

The fact that flunixin can persist in inflammatory tissues is worrisome (ref. #12). No data are provided on the concentration of flunixin in muscles and milk, and its elimination rate from those compartments. Information is also not provided on the biotransformation of flunixin and the activity and toxicity of its metabolites.

(3) the probability of environmental contamination during manufacture, use, misuse or disposal of such substance

The probability of environmental contamination during use or disposal of flunixin is very low. The chemical synthesis of flunixin is not included in the report, and the potential impact to the environment during its manufacture, therefore, cannot be evaluated.

(4) the effect of the substance on human health

The information provided is inadequate to judge the effect of flunixin on human health. The information in the criteria evaluation pertains to NSAID as a class, and is not specific for flunixin. Of particular concern is the probability of hypersensitivity reaction to flunixin in the general human population.

(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

As indicated in the criteria evaluation, use of flunixin under the recommended doses should have negligible or minimal effects on biological and chemical interactions in the agroecosystem.

(6) the alternatives to using the substance in terms of practices or other available materials

The criteria evaluation cited several studies demonstrating that flunixin is more effective in pyrexia and inflammation than several other commonly used compounds, such as phenylbutazone, carprofen, and ketoprofen. However, no information is available on the efficacy of flunixin in comparison to aspirin, a drug that has similar spectrum of activity and is already on the National List.

(7) its compatibility with a system of sustainable agriculture

The information provided in the criteria evaluation is largely correct. However, as indicated earlier in the review, no data are available on the tissue concentration of flunixin and the rate of clearance from the tissue compartment. Based on the doses used, flunixin is more potent than aspirin, but there is no information on comparing the efficacy between the two drugs, which is a more important consideration.

Reviewer 2 Conclusion

Flunixin meglumine (Banamine®) is a synthetic substance that is used for veterinary purposes as an antipyretic, anti-inflammatory, and analgesic drug. Its major mechanism of action is to prevent the synthesis of prostaglandins by inhibiting the enzyme cyclooxygenase.

Flunixin meglumine has been used in horses, beef cattle and non-lactating dairy cattle for control of inflammation and pyrexia. When administered within the recommended doses and by a certified veterinarian, flunixin is effective, safe, and shows no evidence of causing direct harm or adverse effects to the environment or the agroecosystem. However, since it is used primarily for veterinary purposes, the effect of flunixin on human health is poorly documented, especially in terms of hypersensitivity or allergic reactions. This is particularly worrisome in light of the fact that flunixin has been shown to persist in inflammatory tissues. More detailed pharmacokinetic studies need to be done to determine the concentration of flunixin in tissues and its rate of clearance. Finally, aspirin, a safe and proven drug that has identical spectrum of activities as flunixin, is already on the National List. There is no justification for adding flunixin to the List.

Reviewer 2 Recommendation Advised to the NOSB

The substance is Synthetic

For organic farming of cattle, the substance should be Not Allowed Without or Only With Restrictions.

Reviewer 3 [M.D, Ph.D. Nutritional Sciences, Founder and Laboratory Director, Metabolic Screening Laboratory, Professor, Midwest U.S.]

OFPA Criteria Evaluation/ Comments on Report

As Banamine, Flunixin meglumine is a commonly used analgesic- antipyretic for livestock. . Flunixin is a nicotinic acid derivative with an N-linked 2-methyl-3-trifluoromethyl-aniline group attached at carbon 2. The meglumine (N-methylglucamine) counterion is a 1-methylamino-1-deoxy-sorbitol which has its own pharmacologic activity as an anti-protozoal. Although derived from intermediary metabolites, neither of these components occur as natural products. For inclusion on the National Organic List of pharmaceuticals allowable for use in livestock products labelled as "organic" or "made from organic" the trifluoromethyl group is especially troublesome. It is clearly not naturally occurring. Its common use and apparently rapid disappearance from body tissues is irrelevant in a discussion of allowability in organic foods.

If the label of "organic" is to have any meaning and TAP process is to have any credibility in the eyes of the skeptical public, pharmaceuticals such as this must not be allowed. Clear natural product alternatives are available and mentioned in NOSP documents: aspirin and related hydroxyphenyl compounds are effective and naturally occurring and can be given to livestock as willow bark or water extracts. The idea implied in the application that organically-raised livestock might be made to suffer unnecessarily so that their owners might market them under a particular label is sinister and coercive. Obviously, the owners have the alternative of selling sick livestock or moving them to herds not intended for the organic foods market. If safety, pharmacodynamics and popularity were the only criteria used in the NOSB process, it

would rightly be dismissed as a wholly-owned subsidiary of conventional agribusiness. "Organic" must remain what it is in the eyes of the perhaps naïve public--an aesthetic as well as a scientific designation.

The discussion on page 4 of the inflammatory process leaves out the most important step: the release due to cell membrane disruption of fatty acids from phospholipids by phospholipases. The make-up of these membrane phospholipids is dependent on the diet, even in ruminants. If organic cattlemen wish to limit susceptibility of their herds to inflammation in a totally organic way, let them limit the omega-6-fatty acid content of the feeds and assure a trace source of omega-3 fatty acids in the appropriate ratio.

The mention on page 12 of aspirin-glucosamine combinations should be removed because meglumine is not glucosamine which is aminated in the 2-position.

On page 14, the safety profile of NSAIDs is not the issue here. Indeed, if willow bark tea or the anti-inflammatory Chinese tradition medicine RDQ, which we have analyzed by GC-MS in our laboratories, were subjected to rigorous pharmacological studies, their drug interactions and side effect profiles would be far more lengthy and complex than the entire text this TAP report. However, they are definitely "organic" and would so designated by me on historical, botanical and aesthetic grounds.

The discussion on p. 15 of point 5 from the OFPA criteria is completely inadequate as a discussion of the ecological effects of flunixin. At the very least, the source, manufacture, by-products and post-use breakdown products of the trifluoromethyl group should be outlined as exhaustively as for any halogenated hydrocarbon. Likewise, the discussion of point 7 on p. 18 about "sustainable agriculture", to be convincing, would have to outline how some future organic farmer might set up, with the help of her neighbors, a manufacturing operation to produce flunixin meglumine using only things found around the farm. This I would like to see.

Reviewer 3 Recommendation Advised to the NOSB

In summary, I urge the Board to reject the application.