This serves as the response to your Freedom of Information Act (FOIA) request for records regarding adverse event reports received for afoxolaner and fluralaner.

A search of CVM's Adverse Drug Event (ADE) database was performed on 5/31/2016. The search parameters were:

Active ingredient(s):	afoxolaner and fluralaner
Reports received:	From 1/7/2016 through 3/31/2016
Case type:	Spontaneous ADE report
Species:	All
Route of administration:	All

For each drug, we have provided the '**CVM ADE Comprehensive Clinical Detail Report Listing**', which is a cumulative listing of adverse experiences in reports submitted to CVM.

General Information about CVM's ADE Database

The primary purpose for maintaining the CVM ADE database is to provide an early warning or signaling system to CVM for adverse effects not detected during pre-market testing of FDA-approved animal drugs and for monitoring the performance of drugs not approved for use in animals. Information from these ADE reports is received and coded in an electronic FDA/CVM ADE database. CVM scientists use the ADE database to make decisions about product safety which may include changes to the label or other regulatory action. CVM's ADE reporting system depends on detection and voluntary reporting of adverse clinical events by veterinarians and animal owners.

The Center's ADE review process is complex, and for each report takes into consideration confounding factors such as:

- Dosage
- Concomitant drug use
- The medical and physical condition of animals at the time of treatment
- Environmental and management information
- Product defects
- Extra-label (off label) uses

The specifics of these complex factors cannot be addressed in the CVM ADE Comprehensive Clinical Detail Report Listing.

How to Use the CVM ADE Comprehensive Clinical Detail Report Listing

Clinical signs reported for an active ingredient are listed in order from most frequently reported to least frequently reported, grouped by species and route of administration.

More than one clinical sign may have been reported per ADE case report, so the 'Number of times reported' column is not additive and does not necessarily represent the total number of reports received. Also, if a manufacturer reports multiple products in a single ADE case report, clinical signs are associated with each of the manufacturer's products.

Afoxolaner and fluralaner are both approved for oral use in **dogs** only. For the time period of the ADE database search (1/7/2016 – 3/31/2016), there were a total of 505 ADE reports received for afoxolaner for dogs, and a total of 866 ADE reports received for fluralaner for dogs.

The following table shows the number of reports broken down by all species for which reports have been received during this time period:

Species	**# Afoxolaner reports**	**# Fluralaner reports**
Dog	505	866
Cat	2	1
Human (accidental exposures)	3	4
Cattle		1
Rabbit		1
Other (porcupine)		1
Total # ADE reports, all species	510	874

When reviewing the CVM ADE Comprehensive Clinical Detail Report Listing, the reader should be aware that:

- For any given ADE report, there is no certainty that the reported drug caused the adverse event. The adverse event may have been related to an underlying disease, using other drugs at the same time, or other non-drug related causes. The clinical detail listing does not include information about underlying diseases, other drugs used at the same time, other non-drug related causes, or the final outcome of the reaction.
- The accuracy of information regarding the ADE is dependent on the quality of information received from the reporting veterinarian or animal owner.
- Accumulated ADE reports should not be used to calculate incidence rates or estimates of drug risk, because there is no accurate way to determine how many animals were actually given the drug, which is needed as the denominator in calculations of incidence and relative risk.
- It is inappropriate to make use of adverse event data to compare the safety of different products. For example, if a drug is widely used to treat certain conditions, there may be more ADEs for that drug than another product that is not used as often. This would not mean that the first drug was more unsafe than the second.

The number of reports simply represents the number of ADEs received for a particular drug and should not be used for any type of comparison purposes.

- Underreporting occurs with most adverse event reporting systems. The frequency of reporting for a given drug product varies over time, and may be greater when the drug is newly marketed, or when media publicity occurs.
- Information on how the drugs were used (for indications on the product label or in an extra label manner) is not provided in the clinical detail listing.

More information about CVM's ADE Reporting System can be found on our web site at: http://www.fda.gov/AnimalVeterinary/SafetyHealth/default.htm.

CVM ADE Comprehensive Clinical Detail Report Listing

Cumulative Date Range : 07-Jan-2016 -thru- 31-Mar-2016
For case type: Spontaneous

DRUG: FLURALANER

Species: Cat
Route of Administration: ORAL

Sign :	Number of Times Reported :
GLAZED EYE	1

Species: Cattle
Route of Administration: ORAL

Sign :	Number of Times Reported :
VOMITING	1

Species: Dog
Route of Administration: MISSING

Sign :	Number of Times Reported :
HAIR LOSS NOS	1
SKIN DISORDERS NOS	1

Species: Dog
Route of Administration: ORAL

Sign :	Number of Times Reported :
VOMITING	361
LETHARGY	93
DIARRHOEA	67
EMESIS (MULTIPLE)	61
ANOREXIA	30
DECREASED APPETITE	28
LACK OF EFFICACY (ECTOPARASITES)	26
SEIZURE NOS	22
BEHAVIOURAL DISORDER NOS	17

PRURITUS	**16**
ABNORMAL TEST RESULT	**15**
BLOODY DIARRHOEA	**14**
LOOSE STOOL	**14**
ATAXIA	**13**
INAPPETENCE	**12**
HIVES	**11**
POLYDIPSIA	**11**
DEATH	**9**
POLYURIA	**9**
PRODUCT PROBLEM	**9**
SHAKING	**9**
DISORIENTATION	**8**
WEAKNESS	**8**
INAPPROPRIATE URINATION	**7**
WEIGHT LOSS	**7**
ABNORMAL RADIOGRAPH FINDING	**6**
FLATULENCE	**6**
ITCHING	**6**
LEUCOCYTOSIS	**6**
NEUTROPHILIA	**6**
NOT EATING	**6**
PANTING	**6**
RELUCTANT TO MOVE	**6**
RESTLESSNESS	**6**
TREMOR	**6**
ANAEMIA NOS	**5**
ANXIETY	**5**
DROOLING	**5**

ELEVATED ALT	**5**
EMESIS	**5**
FEVER	**5**
LACK OF EFFICACY	**5**
PANCREATITIS	**5**
PUSTULES	**5**
TREMBLING	**5**
DEATH BY EUTHANASIA	**4**
DEHYDRATION	**4**
DERMAL CYST(S)	**4**
HYPERGLYCAEMIA	**4**
NAUSEA	**4**
URINARY INCONTINENCE	**4**
VOCALISATION	**4**
BLOOD IN FAECES	**3**
BREATHING DIFFICULTY	**3**
COLLAPSE	**3**
CRUST	**3**
DEPRESSION	**3**
DERMATITIS	**3**
DRINKING A LOT	**3**
DRY SKIN	**3**
ELEVATED AMYLASE	**3**
FACIAL SWELLING	**3**
GLAZED EYE	**3**
HAIR LOSS NOS	**3**
HYPOALBUMINAEMIA	**3**
LICKING	**3**
LIVER DISORDER NOS	**3**

MONOCYTOSIS	**3**
NOT DRINKING	**3**
PALE MUCOUS MEMBRANE	**3**
RETCHING	**3**
SCRATCHING	**3**
THROMBOCYTOPENIA	**3**
UNCOMFORTABLE	**3**
ABNORMAL BREATHING	**2**
ABNORMAL NECROPSY FINDING	**2**
ABNORMAL STOOL COLOURATION	**2**
ABNORMAL ULTRASOUND FINDING	**2**
AGGRESSION	**2**
AGITATION	**2**
ALOPECIA LOCAL	**2**
BACTERIAL SKIN INFECTION NOS	**2**
BIRTH DEFECT	**2**
BUMPING INTO WALLS	**2**
CIRCLING	**2**
CONSTIPATION	**2**
DECREASED ACTIVITY	**2**
DECREASED DRINKING	**2**
DECREASED RED BLOOD CELL COUNT	**2**
DIGESTIVE TRACT DISORDER NOS	**2**
DRUNKEN GAIT	**2**
ELEVATED AST	**2**
ELEVATED BUN	**2**
ELEVATED CREATININE	**2**
ELEVATED LIPASE	**2**
ELEVATED LIVER ENZYMES	**2**

ELEVATED SAP	**2**
ENLARGED LYMPH NODE	**2**
EPIDERMAL COLLARETTE	**2**
EXCESSIVE THIRST	**2**
FACIAL OEDEMA	**2**
FEMALE REPRODUCTIVE TRACT DISORDER NOS	**2**
FOAMING AT THE MOUTH	**2**
GENERALISED ITCHING	**2**
HAEMORRHAGIC GASTROENTERITIS	**2**
HIDING	**2**
HOT SPOT (PYOTRAUMATIC DERMATITIS)	**2**
HYPERACTIVITY	**2**
HYPERAESTHESIA	**2**
HYPERPHOSPHATAEMIA	**2**
HYPERSALIVATION	**2**
HYPOGLYCAEMIA	**2**
HYPOPHOSPHATAEMIA	**2**
IMMUNE MEDIATED HAEMOLYTIC ANAEMIA	**2**
IMMUNE MEDIATED THROMBOCYTOPENIA	**2**
INAPPROPRIATE DEFECATION	**2**
INCREASED HEART RATE	**2**
LAMENESS	**2**
LISTLESS	**2**
LOW PLATELET COUNT	**2**
LYMPHOMA	**2**
LYMPHOPENIA	**2**
MEDICATION ERROR	**2**
MELAENA	**2**
MOIST DERMATITIS	**2**

MUCOSA PETECHIAE	**2**
MUSCLE ATROPHY	**2**
MUSCLE WEAKNESS NOS	**2**
MYDRIASIS	**2**
OTITIS EXTERNA	**2**
PARALYSIS	**2**
PICA NOS	**2**
PINNAL ERYTHEMA	**2**
PRURITIC RASH	**2**
REDUCED RESPONSES	**2**
REGURGITATION	**2**
SHALLOW BREATHING	**2**
SHIVERING	**2**
SKIN LESION NOS	**2**
SKIN SCAB	**2**
SKIN SORE	**2**
STAR-GAZING	**2**
STIFFNESS NOS	**2**
STOMACH UPSET	**2**
SUDDEN DEATH	**2**
TACHYPNOEA	**2**
UNABLE TO STAND	**2**
UNCLASSIFIABLE ADVERSE EVENT	**2**
URINARY TRACT INFECTION	**2**
WALKING DIFFICULTY	**2**
WEAKNESS OF LIMB	**2**
ABDOMINAL MASS	**1**
ABDOMINAL PAIN	**1**
ABNORMAL MENACE REFLEX TEST	**1**

ABNORMAL POSTURE NOS	**1**
ABNORMAL PUPIL LIGHT REFLEX	**1**
ADIPSIA	**1**
ALLERGIC SKIN REACTION	**1**
ANGIOEDEMA	**1**
APNOEA	**1**
APPETITE LOSS	**1**
AZOTAEMIA	**1**
BELCHING	**1**
BLOOD IN VOMIT	**1**
BRUISING	**1**
CARDIAC DISORDER NOS	**1**
CHEWING	**1**
CLOUDY EYE	**1**
COLD FEELING OF EXTREMITY	**1**
CONFUSION	**1**
CONGENITAL CARDIOVASCULAR DISORDER NOS	**1**
CONGESTED MUCOUS MEMBRANE	**1**
CORNEAL OEDEMA	**1**
COUGH	**1**
CRYPTORCHIDISM	**1**
DECREASED PACKED CELL VOLUME (PCV)	**1**
DIABETES MELLITUS	**1**
DILATED PUPILS	**1**
DISORDER OF RED BLOOD CELL NOS	**1**
DROOPING EYELID	**1**
DULLNESS	**1**
DYSPNOEA	**1**
DYSURIA	**1**

ELEVATED CREATININE-KINASE (CK)	**1**
ELEVATED TOTAL BILIRUBIN	**1**
ENLARGED LYMPH NODE(S)	**1**
ERYTHEMA	**1**
ERYTHEMATOUS RASH	**1**
EXCITATION	**1**
EXOCRINE PANCREATIC INSUFFICIENCY	**1**
FALLING	**1**
FATTY LIVER	**1**
FEBRILE	**1**
FLY BITING BEHAVIOUR	**1**
FOLLICULITIS	**1**
GASTRITIS	**1**
GENERALISED WEAKNESS	**1**
HAEMATEMESIS	**1**
HAEMATOCHEZIA	**1**
HAEMATURIA	**1**
HAEMORRHAGIC BLADDER	**1**
HALITOSIS	**1**
HARSH LUNG SOUNDS	**1**
HEAD SHAKE - BEHAVIOURAL DISORDER	**1**
HEART MURMUR	**1**
HEPATIC DISORDER NOS	**1**
HEPATOMEGALY	**1**
HICCUP	**1**
HIND LIMB ATAXIA	**1**
HIND LIMB PARALYSIS	**1**
HIND LIMB PARESIS	**1**
HYDROCEPHALUS	**1**

HYPERALBUMINAEMIA	**1**
HYPEREXTENSION	**1**
HYPERPROTEINAEMIA	**1**
HYPERTENSION	**1**
HYPOCALCAEMIC CONDITION	**1**
HYPOSTHENURIA	**1**
ICTERUS	**1**
IMPAIRED VISION	**1**
INCREASED APPETITE	**1**
INCREASED PERCENTAGE RETICULOCYTES	**1**
INJECTION SITE ALOPECIA	**1**
INJECTION SITE LUMP	**1**
INJECTION SITE PAIN	**1**
INTESTINAL DISORDER NOS	**1**
ISOSTHENURIA	**1**
ITCHY SKIN	**1**
JAW DISORDER	**1**
JOINT STIFFNESS	**1**
LABOURED BREATHING	**1**
LATERAL RECUMBENCY	**1**
LIP ERYTHEMA	**1**
LIP LICKING	**1**
LOCAL SWELLING (NOT APPLICATION SITE)	**1**
LOCALISED HAIR LOSS	**1**
LOCALISED ITCHING	**1**
LOCALISED PAIN NOS	**1**
LOCALISED RASH	**1**
LYMPHADENITIS	**1**
MACULAR RASH	**1**

MAMMARY GLAND DISORDER NOS	**1**
MUCOUS STOOL	**1**
MUSCLE WASTING	**1**
NOT SLEEPING	**1**
OCULAR DISCHARGE	**1**
OESOPHAGITIS	**1**
OESOPHAGUS OBSTRUCTION	**1**
PACING	**1**
PAIN NOS	**1**
PANCREAS DISORDER	**1**
PASTY STOOL	**1**
PEELING SKIN	**1**
PERITONITIS	**1**
PINNAE DISORDER	**1**
PINNAL REDDENING	**1**
PLATELET DISORDER NOS	**1**
PLEURAL EFFUSION	**1**
POLYPHAGIA	**1**
PREPUTIAL DISCHARGE	**1**
PYLORIC ULCER	**1**
PYODERMA	**1**
RECUMBENCY	**1**
RED BLOOD CELL DISORDER	**1**
REDDENING OF THE SKIN	**1**
RENAL FAILURE	**1**
RESPIRATORY DISTRESS	**1**
SCALE	**1**
SELF TRAUMA	**1**
SKIN IRRITATION	**1**

SKIN PETECHIAE	**1**
SLEEPINESS	**1**
SNEEZING	**1**
SPASTICITY	**1**
SPLENOMEGALY	**1**
STRAINING TO DEFECATE	**1**
STROKE	**1**
STUMBLING GAIT	**1**
SWELLING AROUND EYE	**1**
SWOLLEN FEET	**1**
SWOLLEN LIP	**1**
TARRY OR BLACK STOOL	**1**
THROAT IRRITATION	**1**
THROMBOCYTOSIS	**1**
THROMBOEMBOLI	**1**
TIREDNESS	**1**
TREMOR OF LIMB	**1**
TWITCHING	**1**
UNABLE TO RISE	**1**
UNRESPONSIVE TO STIMULI	**1**
UNSTEADY GAIT	**1**
URTICARIA	**1**
VAGINAL HAEMORRHAGE	**1**
VOCALIZING WHILE SLEEPING	**1**
WELT	**1**
WHEAL	**1**
WHEEZING	**1**

Species: Dog
Route of Administration: UNKNOWN

Sign :	**Number of Times Reported :**

DECREASED APPETITE	**1**
LETHARGY	**1**

Species: Human
Route of Administration: TOPICAL

Sign :	**Number of Times Reported :**
PRURITUS	**2**
SKIN SWELLING	**2**
GENERALISED RASH	**1**
REDDENING OF THE SKIN	**1**
RESPIRATORY DISTRESS	**1**
SKIN IRRITATION	**1**
THROAT CONSTRICTION	**1**

Species: Other
Route of Administration: ORAL

Sign :	**Number of Times Reported :**
ABNORMAL NECROPSY FINDING	**1**
BEHAVIOURAL DISORDER NOS	**1**
BLOATED	**1**
DEATH	**1**
DUODENAL ULCER	**1**
ELEVATED ALT	**1**
ELEVATED AST	**1**
ELEVATED TOTAL BILIRUBIN	**1**
HYPOGLYCAEMIA	**1**
INTESTINAL PERFORATION	**1**
SEPTICAEMIA	**1**

Species: Rabbit
Route of Administration: ORAL

Sign :	**Number of Times Reported :**
VOMITING	**1**