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

A search of CVM's Adverse Drug Event (ADE) database was performed on 7/22/2016. The search parameters were:

Active ingredient(s):	afoxolaner, fluralaner and sarolaner
Reports received:	From 4/1/2016 through 7/15/2016
Case type:	Spontaneous ADE report
Species:	All
Route of administration:	All

For each drug (active ingredient), 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, fluralaner and sarolaner are approved for oral use in **dogs** only. For the time period of the ADE database search (4/1/2016 – 7/15/2016), there were a total of 1245 ADE reports received for afoxolaner for dogs, a total of 2338 ADE reports received for fluralaner for dogs, and a total of 27 ADE reports received for sarolaner 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**	**# Sarolaner reports**
Dog	1244	2335	26
Cat	0	1	1
Human (accidental exposures)	1	2	0
Total # ADE reports, all species	1245	2338	27

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 : 04-Apr-2016 -thru- 15-Jul-2016
For case type: Spontaneous

DRUG: FLURALANER

Species: Cat
Route of Administration: ORAL

Sign :	Number of Times Reported :
VOMITING	1

Species: Dog
Route of Administration: MISSING

Sign :	Number of Times Reported :
ABNORMAL MENACE REFLEX TEST	1
ABNORMAL PUPIL LIGHT REFLEX	1
ABNORMAL TEST RESULT	1
BEHAVIOURAL DISORDER NOS	1
BLINDNESS	1
LENS DISORDER NOS	1
MYDRIASIS	1
RETINAL DEGENERATION	1

Species: Dog
Route of Administration: ORAL

Sign :	Number of Times Reported :
VOMITING	971
LETHARGY	257
DIARRHOEA	197
EMESIS (MULTIPLE)	176
LACK OF EFFICACY (ECTOPARASITES)	126
ANOREXIA	88
DECREASED APPETITE	76

SEIZURE NOS	**68**
PRURITUS	**54**
LOOSE STOOL	**43**
ABNORMAL TEST RESULT	**40**
BLOODY DIARRHOEA	**39**
NOT EATING	**33**
PANTING	**33**
INAPPETENCE	**31**
ELEVATED ALT	**29**
BEHAVIOURAL DISORDER NOS	**28**
DEATH BY EUTHANASIA	**27**
ATAXIA	**24**
ELEVATED SAP	**24**
POLYDIPSIA	**23**
FEVER	**22**
DEATH	**21**
SHAKING	**21**
SCRATCHING	**20**
LACK OF EFFICACY	**17**
DEHYDRATION	**16**
ELEVATED BUN	**15**
NOT DRINKING	**15**
INAPPROPRIATE URINATION	**14**
LEUCOCYTOSIS	**14**
PANCREATITIS	**14**
WEIGHT LOSS	**14**
ABNORMAL RADIOGRAPH FINDING	**13**
DECREASED ACTIVITY	**13**
VOCALISATION	**13**
WEAKNESS	**13**

BLOOD IN FAECES	**12**
DROOLING	**12**
ELEVATED CREATININE	**12**
EMESIS	**12**
FALLING	**12**
PICA NOS	**12**
DEPRESSION	**11**
ELEVATED TOTAL BILIRUBIN	**11**
FLATULENCE	**11**
GENERALISED ITCHING	**11**
HIVES	**11**
INAPPROPRIATE DEFECATION	**11**
ITCHY SKIN	**11**
MEDICATION ERROR	**11**
RELUCTANT TO MOVE	**11**
ABDOMINAL PAIN	**10**
COUGH	**10**
ELEVATED AST	**10**
ELEVATED LIVER ENZYMES	**10**
FACIAL SWELLING	**10**
ITCHING	**10**
MUCOUS STOOL	**10**
POLYURIA	**10**
ERYTHEMA	**9**
HYPERACTIVITY	**9**
LICKING	**9**
PRODUCT PROBLEM	**9**
TWITCHING	**9**
ABNORMAL ULTRASOUND FINDING	**8**
ANAEMIA NOS	**8**

DISORIENTATION	**8**
ELEVATED GAMMA-GLUTAMYL TRANSFERASE (GGT)	**8**
HYPERSALIVATION	**8**
RESTLESSNESS	**8**
URINARY INCONTINENCE	**8**
ABNORMAL STOOL COLOURATION	**7**
AGITATION	**7**
ANXIETY	**7**
BLOOD IN VOMIT	**7**
DRINKING A LOT	**7**
FLAKING SKIN	**7**
MYDRIASIS	**7**
NEUTROPHILIA	**7**
PROTEINURIA	**7**
REDDENING OF THE SKIN	**7**
ABNORMAL NECROPSY FINDING	**6**
ADIPSIA	**6**
CRYING	**6**
DECREASED PACKED CELL VOLUME (PCV)	**6**
DECREASED RED BLOOD CELL COUNT	**6**
DRY MUCOUS MEMBRANE	**6**
DULLNESS	**6**
ELEVATED LIPASE	**6**
GAGGING	**6**
HIDING	**6**
IMMUNE MEDIATED HAEMOLYTIC ANAEMIA	**6**
LABOURED BREATHING	**6**
LAMENESS	**6**
LATERAL RECUMBENCY	**6**
LISTLESS	**6**

LOW PLATELET COUNT	**6**
NEUROLOGICAL SIGNS NOS	**6**
OCULAR DISCHARGE	**6**
RETCHING	**6**
STUMBLING GAIT	**6**
TARRY OR BLACK STOOL	**6**
UNCOMFORTABLE	**6**
BLINDNESS	**5**
BLISTERING	**5**
ERYTHEMATOUS RASH	**5**
FOUND DEAD	**5**
HAIR LOSS NOS	**5**
HEAD BOBBING	**5**
HEAD SHAKE - BEHAVIOURAL DISORDER	**5**
HEAD TREMOR	**5**
LIMB WEAKNESS	**5**
LYMPHOPENIA	**5**
MONOCYTOSIS	**5**
NAUSEA	**5**
PACING	**5**
PAIN NOS	**5**
RENAL FAILURE	**5**
RUBBING	**5**
SKIN SCAB	**5**
STOMACH UPSET	**5**
THROMBOCYTOPENIA	**5**
TREMBLING	**5**
TREMOR	**5**
UNABLE TO RISE	**5**
WALKING DIFFICULTY	**5**

AGGRESSION	**4**
ALOPECIA	**4**
ALOPECIA LOCAL	**4**
COLLAPSE	**4**
CONSTIPATION	**4**
DECREASED DRINKING	**4**
DECREASED URINE CONCENTRATION	**4**
DERMATOSIS NOS	**4**
DISCOLOURED URINE	**4**
EOSINOPHILIA	**4**
EPILEPTIC SEIZURE	**4**
EXCESSIVE THIRST	**4**
EYE DISORDER NOS	**4**
FASCICULATION	**4**
FLY BITING BEHAVIOUR	**4**
GAIT ABNORMALITY	**4**
HEAD TILT	**4**
HIND LIMB ATAXIA	**4**
HYPERALBUMINAEMIA	**4**
HYPOALBUMINAEMIA	**4**
ICTERUS	**4**
LIP LICKING	**4**
LOCALISED RASH	**4**
NYSTAGMUS	**4**
OTITIS EXTERNA	**4**
SLEEPINESS	**4**
SNEEZING	**4**
URINE ABNORMALITIES NOS	**4**
ABDOMINAL DISCOMFORT	**3**
ABDOMINAL MASS	**3**

ABNORMAL BREATHING	**3**
AZOTAEMIA	**3**
BALANCE PROBLEM	**3**
BILIRUBINURIA	**3**
BITING	**3**
BLOOD IN URINE	**3**
CIRCLING	**3**
DECREASED BOWEL MOVEMENTS	**3**
ELEVATED AMYLASE	**3**
ELEVATED CHOLESTEROL (TOTAL)	**3**
FEBRILE	**3**
FREQUENT URINATION	**3**
HAEMATEMESIS	**3**
HAEMATURIA	**3**
HAIR CHANGE	**3**
HAIR SHEDDING	**3**
HOT SPOT (PYOTRAUMATIC DERMATITIS)	**3**
HYPERTHERMIA	**3**
HYPONATREMIA	**3**
HYPOPROTEINAEMIA	**3**
HYPOTHERMIA	**3**
IMMUNE MEDIATED THROMBOCYTOPENIA	**3**
INCREASED HEART RATE	**3**
INCREASED PACKED CELL VOLUME (PCV)	**3**
INTESTINAL DISORDER NOS	**3**
JAUNDICE	**3**
JOINT PAIN	**3**
LIVER DISORDER NOS	**3**
LOCALISED HAIR LOSS	**3**
LOCALISED ITCHING	**3**

LYMPHADENOPATHY	**3**
MOIST DERMATITIS	**3**
MUSCULOSKELETAL DISORDER NOS	**3**
PALE MUCOUS MEMBRANE	**3**
PETIT MAL EPILEPSY	**3**
PINNAL ERYTHEMA	**3**
PUSTULES	**3**
PYODERMA	**3**
PYURIA	**3**
RED BLOOD CELL DISORDER	**3**
RENAL DISORDER NOS	**3**
SKIN WARMTH	**3**
STIFFNESS NOS	**3**
STRANGURIA	**3**
UNABLE TO JUMP	**3**
ABNORMAL POSTURE NOS	**2**
APNOEA	**2**
ARCHED BACK	**2**
BACTERIAL SKIN INFECTION NOS	**2**
BALANCE IMPAIRED	**2**
BLOODSHOT EYE	**2**
BLOTCHY RASH	**2**
BREATHING DIFFICULTY	**2**
BRUISING	**2**
CATARACT	**2**
CHRONIC RENAL FAILURE	**2**
COLITIS	**2**
COLLAPSE OF LEG	**2**
CONGESTED MUCOUS MEMBRANE	**2**
CRYSTALLURIA	**2**

DERMATITIS	**2**
DILATED PUPILS	**2**
DRY SKIN	**2**
ELEVATED RENAL PARAMETERS	**2**
ELEVATED TRIGLYCERIDE	**2**
EYELID INFLAMMATION	**2**
GALL BLADDER & BILE DUCT DISORDER NOS	**2**
GASTROENTERITIS	**2**
GENERAL HAIR LOSS	**2**
GENERAL PAIN	**2**
GENERALISED RASH	**2**
GENERALISED WEAKNESS	**2**
HAEMORRHAGE NOS	**2**
HAIR COAT DISCOLOURATION	**2**
HIND LIMB PARESIS	**2**
HYPERAEMIC MUCOUS MEMBRANE	**2**
HYPERCALCAEMIA	**2**
HYPERGLYCAEMIA	**2**
HYPERKALEMIC CONDITION	**2**
HYPERPIGMENTATION	**2**
HYPERPROTEINAEMIA	**2**
HYPOCALCAEMIC CONDITION	**2**
HYPOGLYCAEMIA	**2**
HYPOPHOSPHATAEMIA	**2**
HYPOSTHENURIA	**2**
ILEUS	**2**
IMPAIRED VISION	**2**
INCOORDINATION	**2**
INCREASED BOWEL MOVEMENTS (FREQUENCY)	**2**
INCREASED SENSITIVITY TO SOUND	**2**

IRRITABILITY	**2**
LIMPING	**2**
LOCAL SWELLING (NOT APPLICATION SITE)	**2**
LOCALISED PAIN NOS	**2**
LYMPHOCYTOSIS	**2**
LYMPHOMA	**2**
MALAISE	**2**
MALODOUR	**2**
MUSCLE ATROPHY	**2**
MUSCLE TREMOR	**2**
NASAL BLEEDING	**2**
ORAL BLEEDING	**2**
PINNAL REDDENING	**2**
PLEURAL EFFUSION	**2**
PULMONARY NEOPLASM	**2**
RED EYE	**2**
RETINAL DEGENERATION	**2**
RETINAL DISORDER NOS	**2**
SCOOTING	**2**
SELF TRAUMA	**2**
SKIN DISORDERS NOS	**2**
SKIN PETECHIAE	**2**
SKIN SORE	**2**
SKIN TUMOUR NOS	**2**
STAR-GAZING	**2**
STRAINING TO DEFECATE	**2**
SUDDEN DEATH	**2**
TACHYCARDIA	**2**
TENSE ABDOMEN	**2**
THORACIC CAVITY DISORDER NOS	**2**

THROMBOCYTOSIS	**2**
TIREDNESS	**2**
UNCLASSIFIABLE ADVERSE EVENT	**2**
URINARY TRACT INFECTION	**2**
WHEEZING	**2**
ABNORMAL RED BLOOD CELL	**1**
ACIDOSIS	**1**
ACUTE RENAL FAILURE	**1**
ALKALINE URINE	**1**
ALLERGIC DERMATITIS	**1**
ALLERGIC PRURITUS	**1**
ALLERGY NOS	**1**
ALOPECIA NOS	**1**
ANAL IRRITATION	**1**
ANISOCORIA	**1**
ANTERIOR UVEITIS	**1**
APPETITE LOSS	**1**
ASCITES	**1**
BARKING	**1**
BASOPHILIA	**1**
BELCHING	**1**
BLOATED	**1**
BLOATED STOMACH	**1**
BONE MARROW DISORDER NOS	**1**
BRADYCARDIA	**1**
BRAIN DISORDER NOS	**1**
BULGING EYE	**1**
CHATTERING OF TEETH	**1**
CILIARY BODY AND CHOROID DISORDER NOS	**1**
CLEFT PALATE	**1**

CLOSED EYELID	**1**
COLD FEELING OF EXTREMITY	**1**
COLLAPSE NOS	**1**
CONFUSED	**1**
CONFUSION	**1**
CONGENITAL EYE DISORDER	**1**
CONGESTION OF MUCOUS MEMBRANE	**1**
CONJUNCTIVITIS	**1**
COUGHING UP BLOOD	**1**
DECREASED RESPIRATORY RATE	**1**
DERMAL CYST(S)	**1**
DERMAL THICKENING	**1**
DISCOMFORT NOS	**1**
DISCUS PROLAPSE	**1**
DISORDER OF RED BLOOD CELL NOS	**1**
DISORIENTED STATE	**1**
DISTENSION OF ABDOMEN	**1**
DRUNKEN GAIT	**1**
DRY MOUTH	**1**
DRY NOSE	**1**
DULL	**1**
DYSPNOEA	**1**
EAR INFECTION NOS	**1**
EAR IRRITATION	**1**
ECCHYMOSIS	**1**
ELECTROLYTE DISORDER	**1**
ELEVATED BILE ACIDS	**1**
ENLARGED LYMPH NODE(S)	**1**
EPIDERMAL COLLARETTE	**1**
EPILEPSY	**1**

EPIPHORA	**1**
EPISTAXIS	**1**
EXERCISE INTOLERANCE	**1**
EXTERNAL EAR DISORDER NOS	**1**
EYE ITCHING	**1**
EYESIGHT TROUBLE	**1**
FACE AND NECK SWELLING	**1**
FACIAL PARALYSIS	**1**
FAECAL INCONTINENCE	**1**
FLUID IN ABDOMEN NOS	**1**
FOOD REFUSAL	**1**
FUNGAL SKIN INFECTION NOS	**1**
GASTRIC ULCER	**1**
GENERAL ILLNESS	**1**
GENERALISED SKIN REACTION	**1**
GLAZED EYE	**1**
GLUCOSURIA	**1**
GROANING	**1**
GUT SOUNDS INCREASED	**1**
HAEMATOCHEZIA	**1**
HAEMOCONCENTRATION	**1**
HAEMORRHAGIC DIARRHOEA	**1**
HARSH LUNG SOUNDS	**1**
HEAD SHAKE - EAR DISORDER	**1**
HEART FAILURE	**1**
HEPATIC DISORDER NOS	**1**
HEPATOMEGALY	**1**
HEPATOPATHY	**1**
HICCUP	**1**
HIND LIMB PARALYSIS	**1**

HORIZONTAL NYSTAGMUS	**1**
HYPERADRENOCORTICISM	**1**
HYPERAESTHESIA	**1**
HYPERPHOSPHATAEMIA	**1**
HYPERSENSITIVITY TO LIGHT	**1**
HYPOKALEAEMIA	**1**
HYPOTENSION	**1**
HYPOTHYROIDISM	**1**
INCREASED BORBORYGMUS	**1**
INCREASED RESPIRATORY RATE	**1**
INCREASED SALIVATION	**1**
INCREASED TESTICLE SIZE	**1**
INCREASED URINE CONCENTRATION	**1**
INJECTION SITE BLEEDING	**1**
INVOLUNTARY MOVEMENT	**1**
IRIS DISORDER	**1**
ISOSTHENURIA	**1**
JAW DISORDER	**1**
JAW PAIN	**1**
JOINT OEDEMA	**1**
LACK OF EFFICACY (ENDOPARASITES)	**1**
LACK OF RESPONSE TO OWNER	**1**
LENS DISORDER NOS	**1**
LESS SOCIAL	**1**
LIMPNESS	**1**
LIVER FAILURE	**1**
LOCALISED OEDEMA (NOT APPLICATION SITE)	**1**
LOOSE BOWEL	**1**
LOSS OF BOWEL CONTROL	**1**
LUMP	**1**

MEGAOESOPHAGUS	**1**
MELAENA	**1**
MENINGITIS	**1**
MENTAL CONFUSION	**1**
METASTATIC NEOPLASIA	**1**
MILK PRODUCTION DECREASE	**1**
MISCELLANEOUS EATING DISORDER NOS	**1**
MOUTH ULCER	**1**
MUCOCUTANEOUS ULCER	**1**
MUCOSA PETECHIAE	**1**
MULTI-ORGAN FAILURE NOS	**1**
MUSCLE SHAKING	**1**
MUSCLE WASTING	**1**
MUSCLE WEAKNESS NOS	**1**
MUSCULOSKELETAL PAIN	**1**
MYOCLONIC JERK	**1**
NASAL CAVITY DISORDER NOS	**1**
NEOPLASIA NOS	**1**
NEUROLOGICAL SYMPTOMS NOS	**1**
NEUTROPENIA	**1**
NT - ENDOCARDIOSIS	**1**
OEDEMATOUS ERYTHEMA	**1**
OTITIS INTERNA	**1**
PADDLING	**1**
PANCYTOPENIA	**1**
PAPULAR RASH	**1**
PAPULE	**1**
PARALYSIS	**1**
PARALYSIS NOS	**1**
PARESIS	**1**

PARTIAL BLINDNESS	**1**
PERINEAL FISTULA	**1**
PERIORBITAL OEDEMA	**1**
PETECHIAE NOS	**1**
PIMPLES	**1**
PINNAL OEDEMA	**1**
POLLAKIURIA	**1**
POLYPHAGIA	**1**
PROPRIOCEPTION DEFICIT	**1**
PRURITIC RASH	**1**
PSORIASIS	**1**
PULMONARY HAEMORRHAGE	**1**
PULMONARY OEDEMA	**1**
PURULENT LESION(S)	**1**
RECTAL HAEMORRHAGE	**1**
RECUMBENCY	**1**
REDUCED RESPONSES	**1**
REGURGITATION	**1**
RESPIRATORY DISCOMFORT	**1**
RESPIRATORY DISTRESS	**1**
RESPIRATORY TRACT DISORDER NOS	**1**
SALIVARY GLAND DISORDER	**1**
SCALE	**1**
SCALY CONDITION NOS	**1**
SICKNESS	**1**
SKIN IRRITATION	**1**
SKIN LESION NOS	**1**
SKIN SWELLING	**1**
SKIN ULCER	**1**
SOMNOLENCE	**1**

SPLEEN AND RETICULO-ENDOTHELIAL SYSTEM DISORDER NOS	**1**
SPLEEN RUPTURE	**1**
SPLENOMEGALY	**1**
STIFFNESS LIMB	**1**
STILLBIRTH	**1**
STOMACH INFLAMMATION	**1**
STRIDOR (UPPER RESPIRATORY; FOR LOWER RESPIRATORY SEE ALSO BRONCHIAL RALE)	**1**
SWELLING AROUND EYE	**1**
SWELLING NOS	**1**
SWOLLEN EYE	**1**
SWOLLEN FEET	**1**
SWOLLEN TONGUE	**1**
SYNCOPE	**1**
SYSTEMIC DISORDER NOS	**1**
TACHYPNOEA	**1**
TENESMUS	**1**
THICKENED EAR CANAL(S)	**1**
THORACIC PAIN	**1**
TONGUE PROTRUSION	**1**
TONIC MUSCLE SPASM	**1**
TOOTH DISORDER	**1**
TRAUMA NOS	**1**
TREMOR OF LIMB	**1**
ULCERATION NOS	**1**
ULCERATIVE DERMATITIS	**1**
UNUSUAL STOOL COLOUR	**1**
URINARY BLADDER DISORDER NOS	**1**
URINARY RETENTION	**1**
URINE LEAKAGE	**1**
UVEITIS	**1**

VESTIBULAR DISORDER NOS	**1**
WART	**1**
WEAKNESS OF LIMB	**1**
WEIGHT GAIN	**1**
YELLOW MUCOUS MEMBRANES	**1**

Species: Dog
Route of Administration: TOPICAL

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

Species: Dog
Route of Administration: UNKNOWN

Sign :	**Number of Times Reported :**
VOMITING	**2**
DIARRHOEA	**1**
UNCLASSIFIABLE ADVERSE EVENT	**1**

Species: Human
Route of Administration: TOPICAL

Sign :	**Number of Times Reported :**
SEIZURE NOS	**1**
UNCONSCIOUS	**1**

Species: Human
Route of Administration: UNKNOWN

Sign :	**Number of Times Reported :**
ASTHMA	**1**
HIVES	**1**