

## **IS BRAVECTO SAFE FOR BREEDING DOGS?**

**(Source of this document: "Does Bravecto Kill Dogs")**

BELOW YOU WILL FIND THE RESULTS OF THE STUDY DONE BY EMPLOYEES OF MSD FOR FDA APPROVAL AND ACTUAL CASES MSD HAS REPORTED TO THE EUROPEAN MEDICINE AGENCY

### RESULTS OF STUDY FOR APPROVAL:

Bravecto was administered orally to intact, reproductively sound male and female Beagles at a dose of up to 168 mg/kg (equivalent to 3X the maximum label dose) on three to four occasions at 8-week intervals. The dogs in the control group (0X) were untreated. There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs) or histopathology findings (adult dogs and puppies). One adult treated dog suffered a seizure during the course of the study (46 days after the second treatment). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions). The following abnormalities were noted in 7 pups from 2 of the 10 dams in only the treated group during gross necropsy examination: limb deformity (4 pups), enlarged heart (2 pups), enlarged spleen (3 pups), and cleft palate (2 pups). During veterinary examination at Week 7, two pups from the control group had inguinal testicles, and two and four pups from the treated group had inguinal and cryptorchid testicles, respectively. No undescended testicles were observed at the time of necropsy (days 50 to 71)."

### CASES REPORTED TO THE EUROPEAN MEDICINE AGENCY.

#### CASE ONE - ORGANS OUTSIDE ABDOMINAL CAVITY

Suspected Adverse Reaction- Bravecto 1000 mg was administered to a pregnant dog in February 2015 and on approximately 18 March 2015, the dog gave birth (her first litter) to 6 puppies. One of these puppies had a birth defect (organs out of the abdominal cavity) and died. No treatment was done. The female dog (dam) was unaffected. The owner also reported cases #2015-BR-00653 and #2015-BR-00654. No more information is expected.

#### CASE TWO - 10 PUPPIES ALL DIED WITHIN 24 HOURS DEVELOPED DROOLING

Suspected Adverse Reaction: Bravecto 1400 mg was administered to a pregnant dog (at 45 days of pregnancy) on 14 Sep 2015. On 27 Sep 2015, when the female was at 58 days of pregnancy, she gave birth to 10 puppies; however, all developed drooling and died 24 hours later. The only potential exposure of the puppies to Bravecto was in utero. No treatment was done and no tests or necropsy were done.

#### CASE THREE - PREMATURE DELIVERY

Suspected Adverse Reaction: Bravecto 112.5 mg was administered to a dog in September 2015 and 15 days before the expected date of birth, this female gave birth to 4 dogs. There was no treatment and the outcome of reaction to the female is unknown.

#### CASE FOUR - PREMATURE DELIVERY

Suspected Adverse Reaction: Bravecto 500 mg was administered to a pregnant female dog in December 2015 and approximately 5 days later, she had premature parturition (at 50 days of gestation) and gave birth to 10 premature puppies. However, all the puppies died (the specific date(s) was/were not reported). No treatment was done and the outcome of the female dog (dam) is unknown. No necropsies were done in the puppies.

#### CASE FIVE - SEVEN PUPPIES DIED AFTER LACTATING - FROM ONE TO THREE DAYS AFTER ADMINISTRATION

Suspected adverse reaction: On 04 Nov 2014 The American Society for the Prevention of Cruelty to Animals reported that 7 pups from a litter of 8 died 0-2 days after their lactating bitch was administered Bravecto (over 44 and up to 88 lbs) on 29 Oct 2014. One pup died during the night on the date of administration. Three pups were found dead by 2pm on 30 Oct 2014 and 3 pups were found dead by 2pm on 31 Oct 2014. No necropsy was performed. The product was not administered with food (ELU- treatment program not respected). The bitch and surviving pup remain asymptomatic.

#### CASE SIX - MULTIPLE DEFORMITIES AND DEATH

Suspect of Adverse Event- Bravecto 500 mg was administered to a dog (pregnant female) in November, 2014 and the dog gave birth (seven puppies) and one of these puppies had hydrocephalic, one had cleft palate, one with malformation of the diaphragm and four were weak. One day after parturition six of these puppies died. No necropsy done. The condition of the mother of the puppies is unknown.

#### CASE SEVEN - LITTER OF SIX ALL DIED WITHIN 5 DAYS OF BIRTH

Suspected Adverse Reaction reported by clinic on 10 Jun 2015. A 5 year old 120 lbs gestating dog was given Bravecto 1400mg on approximately 21 May 2015. The dog is a farm dog that had 6 healthy litters in the past. 6 puppies were born on 28 May 2015. 2 pups were found dead on 29 May, 1 found dead on 30 May, 2 more found dead on 01 Jun. The last one died shortly after (all pups were dead within 5 days of birth).

#### CASE EIGHT - LIMB DEFORMITIES AND DEATH

Suspected Adverse Reaction: On 03 Nov 2015, a MAH sales representative was made aware of a perceived adverse reaction that occurred at a different veterinary clinic after use of Bravecto. The details surrounding this perceived reaction (that fulfill the criteria for a valid adverse event) were obtained on 25 Nov 2015. On this date, a veterinarian stated that 1 adult breeding dog was treated with Bravecto 1400 mg (on an unknown date approximately 1 year ago) and her litter of puppies (litter size unknown) had developed limb deformities (coded as birth defect). All of these affected pups died (coded as perinatal mortality). Necropsies were not performed. Four additional adult female dogs had also received Bravecto, the details of which are captured in linked case.

#### CASE NINE - THREE PUPS DIED WITHIN A FEW DAYS AFTER LACTATING BITCH GIVEN BRAVECTO

Suspected Adverse Reaction: On 11 Feb 2015 a boxer breeder reported that a litter of 9 pups was born on 03 Jan 2015. On 05 Jan 2015, the tails and front dew claws were docked and removed from 8 of the 9 pups in the litter. A dose of Bravecto 1000mg (over 44 and up to 88 lbs) was administered to the dam later on 05 Jan 2015. The breeder reported that 3 pups died between 06 Jan 2015 and 09 Jan 2015. Two of the pups were unthrifty runts in the litter. No necropsies were performed, and no fecal tests or diagnostics were run.

#### CASE TEN - ORGAN OUTSIDE ABDOMINAL CAVITY - TWO DEATHS

Suspected Adverse Reaction- Bravecto 250 mg was administered to a pregnant dog in February 2015 and on approximately 18 March 2015, the dog gave birth (her fourth litter) to 3 puppies. One of these puppies had a birth defect (organs out of the abdominal cavity) and one developed incoordination and both died. No treatment was done. The female dog (dam) was unaffected.

#### CASE ELEVEN - DEATH OF LABRADOR POODLE MIXES

Suspected adverse reaction: On 20 Nov 2015, a veterinarian reported (via a distributor representative and MAH company employee) that he was made aware of reports pertaining to Labrador/Poodle mixes (Labradoodles) that had died after receiving Bravecto (unknown dose, unknown dates of administration). However, details surrounding these perceived reactions are unknown (dates approximated).

#### CASE TWELVE - INTESTINES OUTSIDE OF THE BODY; LIMB WOULD NOT EXTEND; DEATH

Suspected adverse reaction: On 29 Dec 2015, a veterinarian reported that an adult female dog had puppies born with abnormalities after she was dosed with Bravecto 1000 mg (over 44 and up to 88 lbs). The owner obtained the Bravecto from another veterinary hospital. Due to previous leg surgery, the dog underwent surgical implantation of semen at the other facility in Sep 2015, using propofol as the anesthetic. The same day the dog was dosed with its first dose of Bravecto. The dog had a planned C-section on approximately 03 Nov 2015 and had 6 pups. One pup was born with its intestines outside of its body, and it did not survive 24 hours. Another pup had a limb that would not extend but it recovered with hydrotherapy and massage. A third pup died within 24 hours of birth. The dog has had at least one uneventful litter with a different sire previously.