Approval Date: November 7, 1997

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-071

B. Sponsor

Schering-Plough Animal Health
1095 Morris Avenue
Union, New Jersey 07083

C. Proprietary Name

Imizol®

D. Established Name

imidocarb dipropionate

E. Dosage Form, Route of Administration, and Recommend Dosages

IMIZOL® is a 12% solution of imidocarb dipropionate. It contains 120 mg of active imidocarb per milliliter (mL) of solution. It is available in 10 mL rubber stopper vials and is intended for intramuscular or subcutaneous injection. IMIZOL® is to be administered at a rate of 6.6 mg/kg b.w. (3 mg/lb) (i.e. 0.25 mL/10 lb.). Repeat the dose in two weeks for a total of two treatments.

DOSING GUIDE 6.6 mg/kg b.w.

Animal Weight	**IMIZOL® Dosage (mL)**
10 lb. (4.5 kg)	0.25 mL
20 lb. (9.1 kg)	0.50 mL
30 lb. (13.6 kg)	0.75 mL
40 lb. (18.2 kg)	1.00 mL
60 lb. (27.3 kg)	1.50 mL
80 lb. (36.4 kg)	2.00 mL
100 lb. (45.5 kg)	2.50 mL

F. Dispensing Status

Rx

G. Indication

For the treatment of babesiosis in dogs with clinical signs and/or demonstrated Babesia organisms in the blood.

II. EFFECTIVENESS

Dose Selection was based upon the following:

a. The literature and the field studies support the efficacy of a dose range from 4 to 10 mg/kg subcutaneously(SC) or intramuscularly (IM).

b. Safety studies have demonstrated safe levels of Imizol up to 9.9 mg/kg.

c. The dose/dose volume is convenient to calculate based upon the 12% solution (120 mg/mL).

Imidocarb dipropionate has been used throughout the world to treat babesiosis in cattle, sheep, horses and dogs. Imidocarb dipropionate was approved in the United States for treatment of babesiosis in horses (NADA 97-288) on September 12, 1978.

Babesia in dogs is an intra-erythrocytic parasite and can be difficult to diagnose. Several presentations of Babesiosis have been described in dogs. The most common presentation of Babesiosis in the U.S. is the subclinical carrier state. Parasites are rarely seen on blood smears and clinical signs are inapparent unless the dog is stressed or put on corticosteroid therapy. Puppies born to carrier bitches may become clinically ill, with a high mortality rate in untreated puppies. Mortality rates can also be high in immunocompromised adults.[1]

[1] Hoskins, DVM, PhD (Editor). The Veterinary Clinics of North America, Small Animal Practice, Tick Transmitted Disease. January 1991:21(1):103-123.

Techniques for diagnosis of babesiosis include blood smears and detection of antibody titers.

A. Dose Determination

From 1980 through 1984, Imizol® was evaluated in several dose determination studies (Guelfi 1980, 1981; Euzeby 1981; Awaz 1984). Treatment effects of Imizol® (12% w/v aqueous solution) against *Babesia canis* in dogs (n=93) were assessed at dose rates of 0, 1, 2, 3, 4, 5 or 6 mg/kg b.w. These studies are summarized in Table 1.

1. *Imizol® 1 mg/kg b.w*.

   Five (5) dogs with natural infections (n=3; Guelfi 1980) or induced infections (n=2; Euzeby 1981) received 1 mg Imizol®/kg b.w. Two dogs with natural infections recovered, but one relapsed a few days after treatment. The two dogs inoculated with *Babesia canis* and treated with a single injection of Imizol® at this dose rate were not cleared of the parasites in the blood, Table 1, page 4 of this document.

2. *Imizol® 2 mg/kg b.w.*

   Sixty-seven (67) dogs with natural *Babesia canis* infections (Guelfi 1980) were treated with 2 mg Imizol®/kg b.w. Fifty-nine dogs recovered rapidly. Poor to fair results were reported in 8 dogs (relapsed or not in complete recovery). Two (2) dogs died of babesiosis and 3 dogs were not returned by the owners for evaluation. Rapid recovery was noted in most dogs. Some dogs relapsed within six months post-treatment (Guelfi 1981). Guelfi (1981) recommended a higher dose rate.

3. *Imizol® 3 mg/kg b.w.*

   Nine (9) dogs with natural *Babesia canis* infections were treated (Guelfi 1980; Euzeby 1981). All dogs recovered rapidly and there were no relapses or deaths. No parasitemia developed in any of the dogs one month after treatment. One author reported that there were no relapses at 11 months post-treatment.

4. *Imizol® 4 or 5 mg/kg b.w.*

   The treatment effects of Imizol® were assessed in 8 dogs naturally infected with *Babesia canis*. Three dogs received Imizol® at a dose rate of 4 mg/kg b.w. (Euzeby 1981), and 5 dogs received 5 mg/kg b.w. (Euzeby 1981, Guelfi 1980) by intramuscular or subcutaneous injection. All dogs recovered rapidly and no relapses were reported.

5. *Imizol® 6 mg/kg b.w*.

   Nine splenectomized dogs were inoculated with *Babesia canis* (Awaz 1984). Four dogs received treatment with 6 mg Imizol® /kg b.w. by a single intramuscular injection, 4 dogs received an alternative treatment, and one dog served as an untreated control. In the Imizol® group, 3 dogs recovered in a short time following treatment and 1 dog died. All dogs receiving the alternative treatment recovered. The dog which served as the untreated control died of babesiosis.

Note: Guelfi (1980) tested dose rates of 1, 2, 3 and 5 mg Imizol®/kg b.w. A total of 63 dogs treated with an alternative treatment served as controls for each of the dose rate comparisons.

Table 1. Imizol® (12% imidocarb dipropionate) dose determination for treatment of *Babesia canis*. Dose was established from the evaluation of 93 dogs treated with Imizol® [Internal Mallinckrodt Reports (Guelfi 1980; Guelfi 1981; Euzeby, 1981) and scientific publications (Awaz 1984)].

Reference	No of Dogs	Type of Infections	Therapy & Dose	Route	Recovered	Relapse	Deaths	Comments
Guelfi 1980[a]	3	Natural	Imizol®	sc	2	1	0	One dog relapsed within a few days of treatment.
Euzeby 1981	2	Inoculate	1 mg/kg b.w.	im	0	2	0	Dogs received a single treatment within 24 hours of inoculation. Some chemo-immunizing properties were suspected but not definitive. Babesia canis was present in the blood of both dogs.
Guelfi 1980[a]	2	Natural	Imizol®	sc	2	0	0	Rapid recovery. Some parasitemia in young dogs.
Guelfi 1980[a]	65	Natural	2 mg/kg b.w.	sc	57	3	2	No data was available for 3 dogs. Recovery was rapid in most cases. Fair to poor results were reported for 3 dogs which are categorized here as relapses. Two dogs died of babesiosis. A higher dose was recommended.
Guelfi 1981	Follow-up of above cases at six months post-treatment				50	9	1	Nine dogs apparently recovered then relapses occurred 6 months post-treatment. Some owners did not respond to the follow up. One dog died of babesiosis.
Guelfi 1980[a]	2	Natural	Imizol®	sc	2	0	0	Rapid recovery.
Euzeby 1981	7	Natural	3 mg/kg b.w.	im	7	0	0	Recovered within 24 hours. No relapses at 11 months
Euzeby 1981	3	Natural	Imizol® 4 mg/kg b.w.	im	3	0	0	Recovered within 24 hours.
Euzeby 1981	3	Natural	Imizol® 5 mg/kg b.w.	im	3	0	0	Recovered within 24 hours.
Guelfi 1980[a]	2	Natural	-	sc	2	0	0	Rapid recovery.
Awaz 1984	4	Inoculate	Imizol® 6 mg/kg b.w.	im	3	0	1	Dogs recovered rapidly and one dog died shortly after treatment.

Dose Determination Literature Cited

K. B. Awaz, et al. Therapeutic Efficacy of Berenil and Imizol® against Experimental Babesia canis infection in Dogs. Indian J of Parasitology. 1984; 8(1): 111-112

B. **Dose Confirmation**:

A total of 1,031 dogs (10 were controls), from two published reports (Ogunkoya 1981; Bodade 1986) are summarized for dose confirmation, Table 2. Dogs naturally infected with *Babesia canis* received a 12% w/v aqueous solution of Imizol® (imidocarb dipropionate) dosed at the rates of 5 or 6 mg/kg b.w. administered by a single subcutaneous or intramuscular injection.

Ogunkoya (1981) evaluated the effectiveness of Imizol® when administered at a dose rate of 5 mg/kg b.w. All dogs (n=1,011) received a single subcutaneous injection. Two disease categories are reported here: Group 1 consisted of 808 dogs infected with *Babesia canis*, and Group 2 included 203 dogs infected with *B. canis* and concurrently infected with other tick- borne parasites. Treatment with Imizol® resulted in complete recovery of 763 dogs (94.4%) in Group I, and 159 (78.3%) dogs in Group II. At 3 months post-treatment, 25 dogs (0.03%) in Group I relapsed after an apparent recovery. No data was provided as to relapses occurring in Group II. No adverse reactions to Imizol® treatment were reported.

Bodade (1986) evaluated 20 clinically ill pet dogs of various breeds and ages (range 3 months to 7 years). Ten dogs served as untreated controls and 10 dogs received Imizol® at a rate of 6 mg/kg b.w. by intramuscular injection. Antibody titers to *B. canis* were determined for both treated and untreated dogs on a bi-weekly basis for 12 to 24 weeks after treatment. Eight (8) of the 10 dogs treated with Imizol® recovered and were still normal 6 months post-treatment with negative antibody titers. Two (2) dogs relapsed 10 weeks after treatment. Four (4) of the 10 control dogs developed clinical babesiosis and had to be treated, 2 others exhibited self cures and the remaining 4 dogs had positive titers and were asymptomatic carriers. No adverse reactions to Imizol® treatment were reported.

Table 2. Dose confirmation summary. A total of 1,031 dogs from two published reports (Ogunkoya, 1981; Bodade, 1986) are summarized. All dogs were naturally infected with *Babesia canis*. Dogs received a single injection of 12% w/v aqueous solution of imidocarb dipropionate dosed at 5 or 6 mg/kg b.w.

Reference	Treatment	No of Dogs	Dose mg/kg b.w.	Route	Recovered	Relapse	Deaths	Comments
Ogunkoya 1981	Imizol®	808	5	sc	763	25	0	At 6 weeks post-treatment, 20 dogs had detectable parasitemia but were not clinically ill.
Ogunkoya 1981a	Imizol®	203	5	sc	159	0	0	Treatment was reported to be highly effective. No relapse information.
Bodade 1986	Imizol®	10	6	im	10	2	0	Two dogs relapsed 10 weeks post-treatment; 8 dogs were normal at 6 months post-treatment and titers declined until not detectable.
Bodade 1986	Control	10	0	0	2	0	0	All dogs with positive titers but not clinically sick. 4 dogs developed babesiosis and had to be treated, and 6 dogs were considered carriers. Two dogs were self cured.

[a] Dogs were concurrently infected with B. canis and other hemoparasites

Dose Confirmation Literature Cited

P. A. Bodade, O. O. Oduye. Antibody titers in naturally occurring Babesia canis infections in dogs. Revue D' Elevage Et De medicine Veterinaire Des pays Tropicaux. 1986; 39(2): 185-188.

A. B. Ogunkoya, J.B. Adeyanju and Y.O. Aliu. Experiences with the use of Imizol® in treating canine blood parasites in Nigeria. J. Small Anim. Pract. 1981; 22: 775-777.

C. Field Trials:

Clinical effectiveness was demonstrated in two published papers (Irwin 1991, Adeyanju 1982) and one clinical trial conducted in the United States. Results from these two papers and the clinical trial are listed in Table 3. The names of the investigators in the clinical trial are listed in Table 4.

Imizol® was administered at doses of 4 - 5 mg/kg b.w. or 10 mg/kg b.w. to 325 pet dogs with natural infections of only *Babesia canis* or concurrent infections with other hemoparasites (Table 3, page 9). In one paper (Irwin 1991), 8 puppies (4-9 weeks old) served as controls. All eight puppies died of babesiosis. The global distribution of these field cases involves the United States (n=45), Nigeria (n=265), and Australia (n=16 + 8 controls).

Number of Dogs	**Treatment Group**
313	495 mg/kg imidocarb
12	10 mg/kg imidocarb
1	24 mg/kg imidocarb
8	controls

Total of 334 dogs; 326 treated/8 controls

Imizol® was administered at a dose rate of 4 to 5 mg/kg b.w. by intramuscular or subcutaneous injection to a total of 313 dogs. Twelve dogs received 10 mg/kg b.w. Complete recovery or a progressive remission of clinical signs was reported in 90% (294/325) of the cases treated with either 4 to 5 mg/kg or 10 mg/kg of imidocarb. Some owners did not follow-up; therefore, treatment results were unknown for sixteen dogs. Six of the 325 dogs never exhibited clinical signs, therefore were not classified as recovered or relapsed. Two of the 5 mg/kg b.w. imidocarb-treated dogs relapsed after initial recovery.

All eight (8) of the untreated puppies died. One (1) dog which received 24 mg/kg b.w. (accidental overdose) died of Imizol® toxicity. Seven (7) dogs died of babesiosis despite administration of imidocarb at 4-5 mg/kg b.w. None of the dogs which received the 10 mg/kg dose died.

Pain at the time of injection and salivation were frequently reported by veterinarians in the United States. Other transient adverse effects reported were nasal drips, vomiting, panting, agitation, and injection site swelling. Two deaths were reported to be treatment related and were discussed previously (See Table 3). Adeyanju (1982) reported that none of the dogs treated exhibited adverse reactions.

Table 3 Field Trial summary. Dogs naturally infected with *B. canis* alone or concurrently with other tick-borne parasitic diseases were evaluated. Data were obtained from two published papers and one study report (from a U.S. clinical field trial) which demonstrates the effectiveness of Imizol®.

Reference	**No of Dogs**	**Imizol®Dose Rate mg/kg b.w.**	**Route**	**Recovered**	**Relapse**	**Death**	**Comments**
Irwin 1991	8	Controls	0	0	0	8	All were puppies 4-9 weeks old
Irwin 1991	16	5	im	10	No data	4	Four puppies less than 10 weeks old died of babesiosis; Author did not report on all cases.
Adeyanju 1982	260	5	im	249	0	0	95.8% of the dogs recovered. Progressive remission of clinical signs and improvement in hematological values. Parasites were detected in 10 dogs 6 weeks post-treatment..
Adeyanju 1982[a]	5	5	im	3	0	2	60% recovered. Progressive remission of clinical signs and

Reference	No of Dogs	Imizol®Dose Rate mg/kg b.w.	Route	Recovered	Relapse	Death	Comments
							improvement in hematological values. No parasites in the blood at 6 weeks post-treatment.
Clinical Trial 1996	1	4	im	1	0	0	Dog received a second treatment 14 days after the first.
Clinical Trial 1996	31	5	im, sc	25	2	1a	Thirteen dogs received two treatments. Twelve dogs with clinical babesiosis returned to normal. Some owners did not return for follow-up. One dog with a concurrent hemoparasite infection never improved and eventually died.
Clinical Trial 1996	12	10	im, sc	6	0	0	Six dogs did not exhibit pronounced clinical signs of Babesiosis. One dog had a concurrent infection of another hemoparasite and remained the same. Some owners did not return for follow up evaluations.
Clinical Trial 1996	1	24	im	0	0	1	Dog was overdosed and died.

a Dogs were concurrently infected with B. canis and other hemoparasites.

Table 4. List of field trial investigators who contributed to the U.S. clinical field trial:

Steven Bowen, DVM Valley Veterinary Hospital 485 Broadway, Suite F El Centro, CA 92243 619-352-1279	Diane Chesebro, DVM All Animal Clinic 5505 5th Avenue Key West, FL 33040 305-294-5255
Steven Covert, DVM Altamonte Veterinary Hospital 1089 E. Altamonte Drive Altamonte, FL 32701 407-339-1922	Danny Dillon, DVM Kenersville Veterinary Hospital 209-A Century Park Blvd. Kenersville, NC 27284 910-996-3748

Robert Doak, DVM VCA Wyoming Animal Hospital 1300 Wyoming Blvd. N.E. Albuquerque, NM 87112 505-298-7444	Christine Ellis, DVM Arborview Animal Hospital 244 W US Hwy 6 Valparaiso, IN 46383 219-762-7267
Janice Fenichel, DVM ASPCA 424 E. 92nd St. New York, NY 10128 212-876-7700	Joseph Giangarra, DVM Mountain Lore Animal Hospital 765 South End Rd. Southington, CT 06479 860-276-8553
Russell Greene, DVM Phoenix Veterinary Internal Medicine Services 13633 N. Cave Creek Rd. Phoenix, AZ 85022 602-788-2400	Darin Hisanaga, DVM Waipahu Leeward Veterinary Clinic 94-801 Farrington Highway Suite 3 Waipahu, HI 96797 808-671-4095
Gayland Jones, DVM Wabash Valley Animal Hospital 3004 South 7th St. Terre Haute, IN 47802 812-232-5414	Suellen Kotake-Hollars, DVM All Pets Clinic 94-366 Pupupani St. Waipahu, HI 96797 808-671-8424
Vincent LoDuca, DVM Aycock Veterinary Clinic 5490 Stirling Rd. Davie, FL 33314 954-989-8393	Kerlin Nogle, DVM Aerowood Animal Hospital, P.S., Inc. 2975 156th S.E. Bellevue, WA 98007 206-746-6557
H.J. Rebhan, DVM Waianae Veterinary Clinic 85-794 Farrington Hwy Waiamae, HI 96792 808-696-4161	John Robb, DVM New Fairfield Vet Hospital 36 Route 37 New Fairfield, CT 6812 203-746-3041
G.A. Robertson, DVM Levy Pet Clinic 4242 W. 47th St. North Little Rock, AR 72118 501-758-8550	Joanne Woltmon, DVM Kauai Veterinary Clinic 1864 Haleukana Street Lihue, HI 96766 808-245-4748

Field Trials Literature Cited

P. J. Irwin, and G. W. Hutchinson. Clinical and pathological findings of babesia infections in dogs. Australian Veterinary J. 1991; Vol. 68(6):204-209.

B. J. Adeyanju, and Y.O. Aliu. Chemotherapy of Canine Ehrlichiosis and Babesiosis with Imidocarb Dipropionate. J of the AAHA;1982 Sept/Oct, Vol 18:827-830

III. ANIMAL SAFETY

A. Toxicity Study

Imizol was administered to four groups of ten, 9 month-old Beagle dogs at 2.2, 5.5, 7.7 or 9.9 mg/kg b.w. subcutaneously, given twice with two weeks between doses. A control group (ten similar animals) was administered saline in an identical manner.

Imizol® caused pain on injection in nearly all animals, regardless of dose. One injection site reaction (ulceration of injection site) occurred at the highest dose (9.9 mg/kg). Injection site reactions (swelling) after the second injection of Imizol were present in 4 out of the 10 dogs which received the lowest dose (2.2 mg/kg) and in all of the dogs which received the higher doses of Imizol. The dog that developed the injection site ulceration after the first dose of 9.9 mg/kg Imizol also developed injection site ulceration after the second dose of 9.9 mg/kg Imizol.

Post-treatment vomiting was seen in all Imizol-treated groups at a frequency of 1 to 4 out of 10 dogs. The adverse effect was not dose related nor did the dogs respond the same to both injections. These results are consistent with the cholinergic effects attributed to Imizol.

On Days 21, 28 and 35 of the study there was a statistically significant increase in serum alanine aminotransferase (ALT, SGPT) and arginine aminotransferase (AST, SGOT) in the 9.9 mg/kg b.w. as compared to the placebo group. At Day 42, these differences were no longer apparent.

Imizol® had no effects, at any dose level, on body temperature, body weight, hematology, other clinical chemistry values or gross pathology. This study demonstrates that the margin of safety for Imizol® administered to dogs at 6.6 mg/kg b.w. subcutaneously and repeated in two weeks is adequate for its intended use.

B. Tolerance Study

Imidocarb was given orally to three groups of eight, 14 -16 week-old beagle dogs at the rate of 5, 20, or 80 mg/kg daily for 90 days. A fourth group of similar dogs served as untreated controls.

In the 80 mg/kg group, all the male dogs(4) died during the trial and two of the females were euthanized *in extremis*. Their clinical signs included salivation, diarrhea, anorexia, dyspnea, tachycardia, listlessness and weakness. Clinical chemistries showed elevations of serum alanine aminotransferase (ALT, SGPT) and arginine aminotransferase (AST, SGOT) in the 80 mg/kg treated animals just prior to their death. Post mortem examinations revealed moderate to advanced fatty infiltration in the livers of all animals in the 80 mg/kg group. Other findings in this group were inflammation, thickening and congestion of the intestine and stomach. Histopathology of those animals that died or were killed *in extremis* revealed hemorrhagic necrosis of the centrilobular areas of the liver, vacuolation of the hepatocytes in the non-necrotic areas and proliferation of the bile duct epithelium. Fat deposition in Henle's loop and distal convoluted tubules of the

kidney was noted. In addition, pyknosis and karyorrhexis of cells in the thymus, spleen, lymph nodes, liver and villi of the small intestine were seen. Histopathologic findings of the two survivors of this group revealed hepatocyte vacuolation and esoinophilic hyaline globules in centrilobular hepatocytes, but no other significant findings.

In the 20 mg/kg group, all animals had moderate to advanced fatty infiltration of the liver. Other findings were inflammation, thickening and congestion of the intestine and stomach. Histopathology revealed three dogs with hepatocyte vacuolation and two dogs with focal hepatitis.

There were no changes of toxicological significance in the 5 mg/kg group as compared to controls.

The target organs of toxicity were liver and intestines in this study of imidocarb using the oral route of administration.

C. Additional Safety Information:

In a pharmacokinetic study conducted by Abdullah et al (1984), imidocarb was given to dogs intravenously at a dose of 4 mg/kg. One of 13 dogs died on post-treatment Day 8. The dog that died had clinical signs characterized by anorexia, listlessness, dypsnea, tachycardia, weakness and profuse diarrhea. The target organs of toxicity in this dog were lungs and kidneys, and some changes were noted in the liver and spleen. Adverse reactions in all thirteen dogs were salivation and diarrhea.

D. Summary of toxicity:

The toxic syndrome involves lethargy, weakness and anorexia, with possible signs of gastrointestinal, liver, kidney and lung dysfunction.

Literature Cited

A. S. Abdullah, et al. Adverse Effects of Imidocarb Dipropionate (Imizol®) in a Dog. Veterinary Research Communications. 1984 (8):55-59

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. The drug is labeled for use in dogs, which are non-food animals.

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and Part 514 of the implementing regulations (Title 21 of the Code of Federal Regulations). The data demonstrate that Imizol (imidocarb dipropionate), when used under labeled conditions of use, is safe and effective for the treatment of babesiosis in dogs.

Labeling restricts this drug to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine an infection with Babesia organisms.

FDA has determined under [[section]]25.33 (See 62 FR 40570, 40596, July 29, 1997 to be codified at 21 CFR Part 25) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non-food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.