Approval Date: March 25, 1991

# FREEDOM OF INFORMATION SUMMARY

## I. GENERAL INFORMATION

### A. File Number

NADA 134-779

### B. Sponsor

Pfizer, Inc.
235 East 42nd Street
New York, New York 10017

### C. Proprietary Name

Paratect Flex(TM)

### D. Established Name

morantel tartrate

### E. Dosage Form

The Paratect Flex(TM) Diffuser is another dosage form of the Paratect Cartridge, a sustained release solid oral dosage form approved under NADA 134-779 on December 7, 1984. Physically, the Paratect Flex(TM) Diffuser is a resilient laminated sheet with a copolymer core which contains 11.8 grams of morantel (base) activity. A series of holes is punched through the sheet and the sustained release of morantel is through the unsealed sheet edges and exposed core at the holes. The sheet is rolled into a cylindrical shape approximately 1.0" in diameter and 3.75" in length, taped to retain the coiled configuration and the ends sealed with plugs.

### F. Dispensing Status

OTC

### G. Dosage Regimen

The Paratect Flex(TM) Diffuser is to be administered when cattle are turned out onto pasture. Administer orally one Paratect Flex(TM) Diffuser to each weaned calf and yearling weighing at least 200 pounds. The Paratect Flex(TM) Diffuser is to be administered with a special dosing gun.

### H. Route of Administration

The Paratect Flex(TM) Diffuser, like the Paratect Cartridge, is administered orally using a special dosing gun, is retained intraruminally, and morantel is released for approximately 90 consecutive days.

### I. Indication

The Paratect Flex(TM) Diffuser is indicated for control of the adult stage of the following gastrointestinal nematode infections in weaned calves and yearling cattle:

*Ostertagia* spp, *Trichostrongylus axei*, *Cooperia* spp, and *Oesophagostomum radiatum*. Efficacy of the Paratect Flex(TM) Diffuser is dependent upon continuous control of the gastrointestinal parasites for approximately 90 days following administration.

### J. Effect of Supplement

This supplemental application provides an additional dosage form for the Morantel tartrate cartridge (Paratect Cartridge) which has been approved since 1984 under this same NADA.

## II. EFFECTIVENESS

The anthelmintic activity of morantel tartrate against mature gastrointestinal nematode infections of cattle has been demonstrated in NADA's 92-444 and 93-903 for the Rumatel(TM) premix and conventional bolus formulations, respectively. The utility of a sustained release formulation containing morantel against gastrointestinal nematodes was first demonstrated with the Paratect Cartridge, NADA 134-779.

Two pivotal morantel dose determination titration studies were conducted using experimental infections of *Ostertagia ostertagi*, *Cooperia oncophora*, and, in one study, *Trichostrongylus axei*. The effective sustained dosage level of morantel was projected to be approximately 90 mg morantel (base)/head/day. The results of these and six controlled-dose confirmation studies with the Paratect Cartridge are contained in the Freedom of Information Summary for Paratect (NADA 134-779, 49 FR 47831, December 7, 1984) on file in the Dockets Management Branch, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857.

Based on the field evaluations, efficacy, claimed as the control of the adult stage of *Ostertagia* spp, *Trichostrongylus axei* , *Cooperia spp* and *Oesophagostomum radiatum*, is dependent on the continuous control of the claimed parasites for approximately 90 days following product administration. The principle of Paratect Cartridge efficacy is the release of anthelmintically active quantities of morantel during the first 60 to 90 days of grazing in order to reduce pasture larvae contamination and subsequent generations of parasites *in vivo*.

The Paratect Flex(TM) Diffuser is another dosage form of the Paratect Cartridge and efficacy is a function of the rate of morantel release from the formulation. As demonstrated with the Paratect Cartridge, the pioneer product, the targeted sustained dosage rate is approximately 90 mg morantel base/day for at least 90 days. *In vivo* rate-of-release was evaluated for three Paratect Flex(TM) Diffuser lots in three separate studies which utilized the following common protocol in which rates of release were determined at 30, 60, and 90 days post administration:

One Paratect Flex(TM) Diffuser from each lot was administered to each of 30 Holstein calves. Calves were all approximately 10 months of age and mean individual body weights ranged from 196 to 256 kg among trials. For each Paratect Flex(TM) Diffuser lot, ten calves were sacrificed at 30, 60, and 90 days following treatment. Recovery of each Paratect Flex(TM) Diffuser and assay for residual morantel was performed at the time of sacrifice. Calculation of the rate of morantel release over time was based on the difference between initial lot assays and residual morantel for each sacrifice point. All studies were conducted at the Pfizer Animal Health Research Center, Terre Haute, Indiana.

Efficacy was confirmed by monitoring individual animal body weights and fecal oval counts at 14 day intervals throughout the trial as well as through parasite-free tracer calves used to monitor pasture larvae contamination levels.

**Study 1230C-60-85-005**

Conducted by Dr. L. L. Smith of Viroqua, Wisconsin 60 Holstein heifers with a mean initial body weight of 131 kg were allocated to make two equivalent treatment groups. At turnout to pasture one Paratect Flex(TM) Diffuser was administered to each animal in one group selected at random. Each group was maintained for a total trial duration of 168 days on its own pasture area. Ten animals from each group were selected at random at trial termination and evaluated for speciated adult gastrointestinal worm burdens. Efficacy was 80% against O. spp, 97% against *Cooperia* spp, and 86% against *O. radiatum*.

Efficacy was confirmed by monitoring individual animal body weights and fecal ova counts at 14 day intervals throughout the trial as well as through parasite-free tracer calves used to monitor pasture larvae contamination levels.

The pooled results of these three clinical field trials are shown below.

| **PARASITE** | **MEAN (RANGE)** | **% EFFICACY** |
|---|---|---|
| *Ostertagia* spp | 70 | (63-80) |
| *Trichostrongylus axei* | 96 | (96-97) |
| *Cooperia* spp | 93 | (88-97) |
| *Oesophagostomum radiatum* | 96 | (86-100) |

## III. TARGET ANIMAL SAFETY

The Paratect Flex(TM) Diffuser has the same exterior dimensions as the Paratect Cartridge and is administered in the same way with a special dosing gun. The indications for use and the conditions of use for the two products are also identical including the minimum body weight restriction for administration of 200 pounds.

The safety of administration of the Paratect Flex(TM) Diffuser was confirmed in Study 5431C-03-87-022 conducted by D. J. Shanks of Pfizer Central Research at the Pfizer Breach Farm in Barham, Kent, U.K. One hundred Hereford-Friesian cross calves in a weight range of 85 to 95 kg (187 to 209 lb) were each administered one Paratect Flex(TM) Diffuser without incident. No adverse reactions were observed in any of the calves at the time of dosing or on examination 30 minutes and 24 hours after treatment.

The safety of Paratect Flex (TM) Diffuser administration and long-term toleration were evaluated in Study 543 IE-03-85-001 conducted by Dr. W. T. R. Grimshaw of Pfizer Central Research at the Pfizer Sandwich Kent, U.K. facility. One Paratect Flex(TM) Diffuser was administered to each of 45 Hereford-Friesian cross calves with individual body weights between 110 and 130 kg. No adverse effects were observed at the time of treatment. Ten calves were sacrificed 90 days post- treatment and 32 calves at 12

months post-treatment. Three calves died during the study from non-treatment related disorders. No animal evidenced any observable adverse effect or lesion related to treatment. Intact Paratect Flex(TM) Diffusers were recovered from all animals sacrificed at 90 days and from three animals after 12 months. The Paratect Flex(TM) Diffuser drug-depleted matrix apparently gradually disintegrated between 90 days and 12 months as either no Paratect Flex(TM) Diffuser or only fragments were found in the other animals.

The long-term toleration and fate of the Paratect Flex(TM) Diffuser were evaluated in Study 5431E-03-86-019 conducted by Dr. A. J. Weatherley of Pfizer Central Research at Pfizer's Breach Farm test facility at Barham, Kent, U.K. One Paratect Flex(TM) Diffuser was administered without incident to each of 200 Friesian, Hereford or Hereford-Friesian cross calves weighing between 135 and 170 kg body weight. One hundred of these calves were sacrificed between 181 and 185 days following treatment with the Paratect Flex(TM) Diffuser matrix recovered intact from 96. There was no indication of any irritation or other adverse effect related to the use of the Paratect Flex(TM) Diffuser. The remaining animals were held for future evaluation.

The originally approved Paratect Cartridge (containing 13.5 g morantel base) has the same exterior dimensions as the Paratect Flex(TM) Diffuser (11 g base). Paratect Flex(TM) Diffuser was tested at the recommended therapeutic dosage in the above studies. No additional studies with elevated dosages were conducted because the safety of morantel tartrate was adequately demonstrated in the original application by using Paratect Cartridges at 5x the therapeutic dose.

## IV. HUMAN FOOD SAFETY

### A. Toxicology Data

No new or additional toxicology data were generated or submitted in support of this application. Data from reproductive and genetic toxicology studies as well as acute, subacute, and chronic conventional toxicology studies were summarized in the Freedom of Information Summary for the Paratect Cartridge, NADA 134-779; on file in the Dockets Management Branch (49 FR 47831, December 7, 1984). Subsequent to this approval, additional data were filed in support of higher morantel tissue residue safe concentrations for the morantel tartrate bolus, NADA 93-903, and premix, NADA 92-444, formulations (51 FR 9005, March 17, 1986).

The safe concentrations of morantel tartrate residues and the marker tolerances as codified in 21 CFR 556.425 are based on a No-Observed-Effect-Level of 10 mg/kg/day in a rat teratology study.

### B. Safe Concentration of Residues

The morantel tartrate safe residue concentrations and marker tolerances for all morantel formulations are codified in 21 CFR 556.425. Residue concentrations are determined by measuring morantel residues convertible to MAPA. The tolerance for MAPA, expressed as morantel base, is established in cattle at 0.70 parts per million (ppm) in liver, the target tissue. A marker residue concentration of 0.70 ppm in liver corresponds to a concentration of total residues of morantel tartrate of 2.40 ppm in liver. Tolerance refers to a concentration of a marker residue selected to monitor for total residues of the drug in the target species. Safe concentrations refer to the

concentrations of total residues considered safe in edible tissues and milk. (Reference: 51 FR 9005, March 17, 1986).

## C. Total Residue Depletion and Metabolism Studies and Tolerance for the Marker Residue

The approved residue safe concentrations and the marker tolerances which apply to all morantel tartrate formulations are codified in 21 CFR 556.425.

Total residue and marker depletion kinetics as well as appropriate comparative metabolism data have been the subject of approvals for the conventional morantel tartrate formulations published in 51 FR 9005, March 17, 1986 and, originally, in 46 FR 50949, October 16, 1981. The initial approval of a morantel sustained release formulation was for the Paratect Cartridge in 49 FR 47831, December 7, 1984. The withdrawal period for Paratect was decreased from 160 to 106 days subsequent to a review using contemporary standards of all morantel toxicology and metabolism data with amendment of 21 CFR 520.1450b (the Paratect Cartridge) cited in 51 FR 41081, November 13, 1986.

## D. Study Establishing the Withdrawal Period

Residue depletion Study 1531 N-60-87-018, conducted by E. F. Illyes at the Pfizer Animal Health Research Center at Terre Haute, Indiana, evaluated the depletion characteristics of morantel related residues following treatment with the Paratect Flex(TM) Diffuser. Test conditions were patterned after a similar study which was the basis for approval of the Paratect Cartridge. One Paratect Flex(TM) Diffuser was administered to each of 12 heifer and 12 steer calves. The test animals were of Hereford beef stock, between 14 and 17 months of age with a mean group body weight of approximately 350 kg. Two additional, nonmedicated control animals were maintained concurrently to provide blank tissues for analytical use. Six Paratect Flex(TM) Diffuser treated animals, three of each sex, were sacrificed at 102, 106, 110, and 114 days following treatment and one control animal at 102 days. From each animal, a 250 g sample of liver, the target tissue for morantel, was harvested and submitted to the Drug Metabolism Research and Development Department at Groton, Connecticut for assay of morantel related residues via the marker, MAPA. Throughout the study, no evidence of adverse effect related either to the Paratect Flex(TM) Diffuser formulation or morantel was observed. Mean liver residues expressed as morantel (base) via MAPA were as follows:

Mean morantel released at the 30, 60 and 90 day monitoring points across the three trials was 3.5 g, 6.9 g, and 9.8 g, respectively. The overall mean daily morantel release rate over 90 days was 109 mg. For each lot the release rate coefficient of variation over 90 days was less than or equal to 7%.

To confirm anthelmintic activity against patent infections, a controlled study using experimental infections of *Ostertagia ostertagi* and *Cooperia oncophora* was conducted by Dr. W. T. R. Grimshaw at Pfizer's Animal Health Research facility, Sandwich, Kent, U.K. Two groups of 15 parasite naive calves were experimentally infected and one group treated with one Paratect Flex(TM) Diffuser/calf 23 days later. One week following treatment, adult parasite burdens were reduced by 95 and 96%, respectively, for the two genera.

The above study, in conjunction with the following three dose confirmation studies, serve as pivotal trials and were conducted to confirm efficacy of the Paratect Flex(TM) Diffuser under actual use conditions. For each study and claimed parasite species, efficacy was calculated using the formula:

$$\frac{(Mean\ Control\ Worm\ Burden) - (Mean\ Paratect\ Flex(TM) Diffuser\ Worm\ Burden)}{(Mean\ Control\ Worm\ Burden)} \times 100$$

**Study 1230C-60-85-002**

Conducted by E. F. Illyes at the Pfizer Animal Health Research Center in Terre Haute, Indiana, 60 yearling Hereford steers with a mean body weight of 210 kg were allocated to two equivalent treatment groups. At turnout to pasture one Paratect Flex(TM) Diffuser was administered to each animal in one group selected at random. Each group was maintained on its own pasture areas. Ten animals from each group were sacrificed after 168 days on pasture with determination of speciated adult gastrointestinal worm burdens. Efficacy was 63% against *Ostertagia* spp. (*O*. spp.), 97% against *Trichostrongylus axei* (*T. axei* ), 88% against *Cooperia* spp. (*C.* spp.), and 100% against *Oesophagostomum radiatum* (*O. radiatum*).

Efficacy was confirmed by monitoring individual animal body weights and fecal ova counts at 14 day intervals throughout the trial as well as through parasite-free tracer calves used to monitor pasture larvae contamination levels.

**Study 1230C-60-85-004**

Conducted by Dr. G. L. Zimmerman at the Oregon State University Beef Ranch in Corvallis, Oregon 60 Hereford-Angus type steers with a mean initial body weight of 206 kg were allocated to make two equivalent treatment groups. At turnout to pasture one Paratect Flex(TM) Diffuser was administered to each animal in one group selected at random. Each group was maintained for a total trial duration of 168 days following treatment on its own pasture areas. Ten animals from each group were selected at random after 168 days on pasture with subsequent determination of speciated adult gastrointestinal worm burdens. Efficacy was 68% against *O*. spp. 96% against *T. axei* , 93% against *Cooperia* spp, and 100% against *O. radiatum*.

| **WITHDRAWAL TIME** | **MEAN RESIDUES (PPM)** |
|---|---|
| 102 | 0.24 |
| 106 | 0.23 |
| 110 | 0.20 |
| 114 | 0.19 |

The tolerance for morantel (base) via MAPA in cattle liver is 0.70 ppm. The residues at all time points monitored are well below, less than one-half, the tolerance. Also, the statistical distribution according to the tolerance limit model designed to project the upper 99% of the population with 95% confidence was below tolerance. This study documents a gradual depletion rate but at very low residue concentrations.

Application of a 102 day withdrawal period assures levels of residues below safe concentrations.

The validated regulatory analytical method for detection of the morantel marker, MAPA, is filed in the Food Additives Analytical Manual on display in the Food and Drug Administration's Freedom of Information Public Room (Room 12A-30, 5600 Fishers Lane, Rockville, Maryland 20857).

## V. AGENCY CONCLUSIONS

The data submitted in support of this supplemental NADA satisfy the requirements of section 512 of the Act and demonstrate that Paratect Flex(TM) Sustained Release Diffuser Cattle Anthelmintic when used under its proposed conditions of use is safe and effective.

Additional data regarding manufacturing, residue depletion, target animal safety (regarding the Trilaminate dispenser) and efficacy were submitted in support of this supplemental application. The data submitted was adequate to support approval including the same as those currently approved for the Paratect Cartridge®. These claims are for the control of the adult stage of the following parasites: *Ostertagia* spp., *Trichostrongylus axei* , *Cooperia* spp., and *Oesophagostomum radiatum*.

The Paratect Flex(TM) diffuser for cattle is an alternate sustained release dosage form of the approved Paratect Cartridge®. Under the agency's policy for supplements to approved NADAs, the Paratect Flex(TM) Diffuser represents a change in drug formulation and is a Category 11 change. See 55 FR 46045, 46048, 46052; November 1, 1990 (adding 21 CFR 514.106 (b)(2)). The supplement does not involve a change in the route of administration, however, the agency has concluded that the qualitative composition of the residue remaining in edible tissue will not be altered. In order to limit the quantitative exposure to residues from this new dosage form of morantel tartrate, a withdrawal period of 102 days is established for the product. The 102 day withdrawal period was determined from a residue depletion study and will ensure that there is no increased human risk from exposure to residues of morantel tartrate. The supplement, accordingly, is approved without reevaluation of the underlying human safety and effectiveness data contained in the parent application.

While the Paratect Flex(TM) Diffuser is a new system for the long-term sustained release of morantel tartrate, other types of sustained release systems are currently on the market for use in food animals. Accurate diagnosis can be made with a reasonable degree of certainty by the layman. Adequate directions for use have been written for the layman, and the conditions for use prescribed on labeling are likely to be followed in practice. Therefore, the Center for Veterinary Medicine has concluded that this product remain under over-the-counter marketing status.

Under section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this supplemental approval qualifies for three (3) years of marketing exclusivity beginning on the date of the approval letter before new clinical or field studies were required for the approval.

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.