Date of Approval: June 4, 2024

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 138-255

IRON DEXTRAN 20% INJECTION

(iron hydrogenated dextran injection)

Injectable Solution

Swine, nursing piglets

This supplement provides for a new strength (200 mg/mL) and dose (200 mg/piglet) of the injectable solution.

Sponsored by:

Sparhawk Laboratories, Inc.

Executive Summary
IRON DEXTRAN 20% INJECTION (iron hydrogenated dextran injection) is approved for the prevention or treatment of anemia due to iron deficiency in nursing piglets. The drug is classified as a hematinic because iron is required for hematopoiesis. IRON DEXTRAN 20% INJECTION contains 200 mg of elemental iron per mL (200 mg/mL) and piglets are given 1 mL by intramuscular injection. Iron hydrogenated dextran injection is already approved under the same New Animal Drug Application (NADA) number at a concentration of 100 mg of elemental iron per mL (100 mg/mL) and dose of 100 mg/piglet.

Safety and Effectiveness
The Food and Drug Administration (FDA) did not require the sponsor to conduct effectiveness studies for this supplemental approval. The Freedom of Information (FOI) Summary for the original approval of iron hydrogenated dextran injection at a concentration of 100 mg/mL and dose (100 mg per piglet) contains a summary of studies that demonstrate the drug's effectiveness for preventing and treating anemia in nursing piglets.

The sponsor conducted a margin of safety study in healthy, crossbred, male and female, nursing piglets. IRON DEXTRAN 20% INJECTION was administered at 1X, 2X, and 3X the labeled dose on Days 0 and 7 (2X the labeled duration of one injection). The control group (0X) received another FDA-approved iron dextran product (200 mg) on Day 0 for routine health management but did not receive an injection on Day 7. On Day 0, all piglets were 1 day old.

Compared to piglets in the control group, piglets in the 1X, 2X, and 3X groups had increased mean hemoglobin, mean hematocrit, and mean corpuscular hemoglobin by Day 7. These hematological changes indicated increased blood cell production. Piglets in the 1X, 2X, and 3X groups also had increased iron, total iron binding capacity, and unsaturated iron binding capacity compared to piglets in the control group by Day 14. Both the hematological and serum chemistry changes showed a normal response to iron supplementation in nursing piglets. No significant adverse safety findings were noted in any of the piglets, and none of the piglets showed clinical signs of iron toxicosis.

Human Food Safety
Because iron dextran is not an antimicrobial drug and does not have known antibacterial activity, FDA determined that a microbial food safety assessment was not required.

In the original approval of NADA 138-255, FDA determined that there is no human food safety concern for residues resulting from the use of iron hydrogenated dextran injection at a dose of 100 mg per piglet. Current understanding of the role of iron in human health reinforces the agency's conclusion that, even at a dose of 200 mg per piglet, there is no human food safety concern regarding residues of iron dextran.

FDA determined that it is not necessary to establish an acceptable daily intake or tolerances for residues of iron dextran in edible tissues and that a withdrawal period is not required. An analytical method for detecting iron dextran residues is also not required.

Conclusions
Based on the data submitted by the sponsor for the approval of IRON DEXTRAN 20% INJECTION, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 138-255

B. Sponsor

Sparhawk Laboratories, Inc.
12340 Sante Fe Trail Dr.
Lenexa, KS 66215

Drug Labeler Code: 058005

C. Proprietary Name

IRON DEXTRAN 20% INJECTION

D. Drug Product Established Name

iron hydrogenated dextran injection

E. Pharmacological Category

Hematinic

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

200 mg elemental iron per mL

H. How Supplied

100 mL multidose vial

I. Dispensing Status

Over the counter (OTC)

J. Dosage Regimen

For the prevention of iron deficiency anemia, administer 1 mL (200 mg) at 1-3 days of age.

For the treatment of iron deficiency anemia, administer 1 mL (200 mg) at the first signs of anemia.

K. Route of Administration

Intramuscular injection

L. Species/Class

Swine, nursing piglets

M. Indication

IRON DEXTRAN 20% INJECTION is intended for the prevention or treatment of anemia in nursing piglets due to iron deficiency.

N. Effect of Supplement

This supplement provides for a new strength (200 mg/mL) and dose (200 mg/piglet) of the injectable solution.

II. EFFECTIVENESS

CVM did not require effectiveness studies for this supplemental approval. Substantial evidence of effectiveness was established at the 100 mg/piglet dose therefore no additional effectiveness information was required for the 200 mg/piglet dose. The FOI Summary for the original approval of NADA 138-255, dated April 8, 1985, contains a summary of studies that demonstrate effectiveness of the drug for nursing piglets.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study

Title: Margin of Safety Study with Iron Dextran 20% Injection in Nursing Piglets at Multiples of the Proposed Dose. Study No. MCL 20003.

Study Dates: April 21, 2021 to November 22, 2021

Study Location: Oakland, Nebraska

Study Design:

Objective: To evaluate the margin of safety of Iron Hydrogenated Dextran 20% (200 mg/mL) injection in nursing piglets, and to identify any toxic effects associated with product overdoses and increased intervals of usage.

Study Animals: Twelve sows were acclimated to farrowing crates upon arrival at the study site, of those 12 sows, 6 sows (crossbred Landrace) each farrowed at least 11 healthy piglets [crossbred Landrace (sow) and crossbred Duroc (boar)] on the same day (Day -1). Eight of the 11 piglets from each litter were selected for enrollment (N = 48 piglets total). Twelve piglets were enrolled in each of the 4 treatment groups (See Table III.1.) to achieve at least 8 piglets for scheduled postmortem procedures on Day 14. All enrolled piglets weighed ≥1.0 kg and met enrollment criteria based on physical examinations and evaluations that occurred on Day -1 and Day 0. Piglets of both genders (intact boars and gilts) were enrolled.

Experimental Design: This was a randomized, masked, nonclinical laboratory study, with a multi-tier and multi-time dosing scheme. Within each litter, two piglets were randomly assigned to each of the four treatment groups. A total of 12 piglets total per treatment group were enrolled. Extra piglets that were not enrolled in the study were

removed from the sow prior to treatment administration on Day 0. The piglet was the experimental unit.

The study was conducted according to Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies.

Table III.1. Treatment Groups

Group (Dose)	Piglets per Group	Product	Day 0 dose and volume (IM left ham)	Day 7 dose and volume (IM right ham)
Group 1 (0X)	12	FDA-approved iron dextran product* (untreated)	None*	None
Group 2 (1X)	12	Test Article	200 mg (1.0 mL)	200 mg (1.0 mL)
Group 3 (2X)	12	Test Article	400 mg (2.0 mL)	400 mg (2.0 mL)
Group 4 (3X)	12	Test Article	600 mg (3.0 mL)	600 mg (3.0 mL)

* Piglets received an approved 200 mg/mL iron dextran product on Day 0 in the left ham muscle as a matter of routine health management.

Drug Administration: IRON DEXTRAN 20% INJECTION was administered intramuscularly (IM) to piglets in Groups 2 (1X), 3 (2X) and 4 (3X) on Day 0 (left ham muscle) and Day 7 (right ham muscle). Group 1 (0X) received an FDA-approved iron dextran product (200 mg) on Day 0 (left ham muscle) for routine health management and did not receive any injection on Day 7 (untreated). At initial treatment (Day 0) piglets were one day of age.
Measurements and Observations: The variables of interest included: daily injection site observations, daily clinical observations, twice daily general health observations, physical examinations on Days -1, 0, 2, 7, and 14; body weight on Days -1, 0, 7, and 14; hematology and serum chemistry from blood samples collected on Days 0, 2, 7, and 14; urinalysis on Day 14; fecal examinations on Days -1, 0, 2, 5, 8, and 11; bone marrow smear evaluation after euthanasia on Day 14; and gross pathology and histopathology of target tissues after euthanasia on Day 14.

Statistical Methods:

Descriptive statistics were presented for each variable of interest and time-point for each dose level. All tests of significance were performed at alpha=0.10, two-sided.

Endpoints measured only once during the study (organ weights) were analyzed using a mixed model analysis of variance (ANOVA, the MIXED procedure in SAS) with the classification variable of dose as a fixed effect. If the dose effect was significant ($p \leq 0.10$), pairwise comparisons to Group 1 were constructed using linear contrast statements for each time-point.

Endpoints measured pre-treatment and at multiple times following the first treatment (physical examination measurements, body weights, hematology, and serum chemistry) were analyzed using a mixed model repeated measures analysis of covariance (ANCOVA, the MIXED procedure in SAS). The model included fixed effects of dose, time-point, and dose by time-point interaction. The baseline value was included in the model as a covariate. The covariance structure that provided the smallest Akaike's Information Criterion (AIC) value was used.

Given the unequal interval measurement time-points, the covariance structures that were tested included Compound Symmetry (CS), heterogeneous CS (CSH), and spatial power (SP(POW)). A representative variable within a group of variables was used for the assessment of the AIC.

If the dose by time-point interaction was significant ($p \leq 0.10$), each dose was compared to the control at each time-point using linear contrast statements.

If the dose by time-point interaction was not significant ($p > 0.10$), the main effect of dose was evaluated. If the dose was significant ($p \leq 0.10$), each dose was compared to the control, pooled across time-points, using linear contrast statements.

No hypothesis testing was conducted on the urinalysis results or categorical endpoints.

Results:

a. General Health and Clinical Observations: General health observations were normal for all sows from arrival at the test facility (Sow Acclimation Phase), Farrowing (Day -1) through study completion (Day 14). Clinical observations for all enrolled piglets were normal except for one 1X piglet that was documented as depressed and dehydrated 6 hours post-administration, and moribund and euthanized seven hours post-administration on Day 0. Physical examinations post-administration were normal except for one 1X piglet which was found dead in the pen on Day 2, and one 2X piglet with a laceration in the axillary space of the right front leg on Day 14, prior to the completion of the study and euthanasia. These three abnormalities were determined to not be related to the test article and likely related to trauma caused by the sow.

   In the 1X, 2X, and 3X treatment groups there was visible discoloration (documented as "bruising") of the skin surrounding the injection site following each administration. The 0X treatment group that received the FDA approved iron dextran product (200 mg/mL) on Day 0 also were observed as having visible discoloration of the ham muscle following administration. The visible discoloration resolved within 3 days after Day 0 dosing in all treatment groups, and after 1 day following Day 7 dosing in the 1X, 2X, and 3X treatment groups. No discoloration was observed at Day 14.

   All piglets gained weight from birth to Day 14, and mean body weights were not significantly different across treatment groups.

b. Clinical Pathology: Hematological changes attributable to the test article occurred in hemoglobin (Hb), hematocrit (HCT), mean corpuscular hemoglobin (MCH),

and mean corpuscular volume (MCV). Specifically, the mean Hb and HCT on Day 7 in the 2X and 3X groups, and on Day 14 in the 1X, 2X, and 3X groups, were statistically different than those in the control group (Table III.2.). Mean MCH and MCV in the 1X, 2X, and 3X groups on Day 7 and 14 were statistically different than those in the control group (Table III.3.). These changes were indicative of blood cell production and determined to be a normal response in healthy piglets receiving iron injection supplementation. Bolded values in the tables below infer statistical significance.

Table III.2. Hemoglobin (Hb) and Hematocrit (HCT) Summary

Group (Dose)	Day	LS Mean Hb (g/dL)*	P-value Hb	LS Mean HCT (%)†	P-value HCT
Group 1 (0X)	7	9.5082	---	32.6625	---
Group 2 (1X)	7	9.8985	0.1060	33.6785	0.2701
Group 3 (2X)	7	10.0235	**0.0262**	34.4889	**0.0387**
Group 4 (3X)	7	10.1945	**0.0034**	34.7748	**0.0175**
Group 1 (0X)	14	10.2915	---	34.7208	---
Group 2 (1X)	14	12.6085	**<.0001**	41.7185	**<.0001**
Group 3 (2X)	14	12.7735	**<.0001**	42.6389	**<.0001**
Group 4 (3X)	14	13.0278	**<.0001**	43.5082	**<.0001**

*Reference Range Hb: Day 7: 8.67-9.15, Day 14: 9.67-10.28
† Reference Range HCT: Day 7: 30.66-32.27, Day 14: 33.07-34.99

Table III.3. Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Volume (MCV) Summary

Group (Dose)	Day	LS Mean MCH (pg)*	P-value MCH	LS Mean MCV (fL)†	P-value MCV
Group 1 (0X)	7	22.8196	---	78.6584	---
Group 2 (1X)	7	24.0508	**0.0009**	81.7506	**0.0502**
Group 3 (2X)	7	24.4649	**<.0001**	83.9824	**0.0005**
Group 4 (3X)	7	24.7207	**<.0001**	84.4338	**0.0002**
Group 1 (0X)	14	19.9529	---	67.4500	---
Group 2 (1X)	14	23.8208	**<.0001**	78.6506	**<.0001**
Group 3 (2X)	14	23.8065	**<.0001**	79.4158	**<.0001**
Group 4 (3X)	14	23.9623	**<.0001**	80.3088	**<.0001**

*Reference Range MCH: Day 7: 20.73-21.89, Day 14: 18.64-19.61
† Reference Range MCV: Day 7: 73.19-77.30, Day 14: 63.71-66.94

Serum chemistry changes attributable to the test article occurred in iron, total iron binding capacity, and unsaturated iron binding capacity, and determined to be a normal response in piglets receiving iron injection supplementation.
No findings related to the test article were noted in the bone marrow smear evaluations.

The differences in fecal analysis between treatment groups were not considered to be dose related. Positive results for the presence of occult blood in the fecal samples occurred on all post-sampling days (Days 2, 5, 8, and 11), for 2 piglets in the 0X group, 5 piglets in the 1X group, 3 piglets in the 2X group, and 5 piglets

in the 3X group. Occult blood found sporadically in the stool samples were likely false-positive results due to the ferrous-containing compounds in the test article. There were no treatment related differences in urinalysis results.

c. Postmortem Observations: Postmortem macroscopic abnormalities related to the test article at Day 14 necropsy were limited to the right ham injection sites in the 2X and 3X groups. Yellow discoloration of the surface musculature appeared macroscopically in two piglets in the 2X group and six piglets in the 3X group. This correlated with minimal infiltrates of pigmented macrophages in the muscle, dermis, and/or subcutis and "bruising" visibly observed and documented after injection. Microscopically, all groups treated (0X, 1X, 2X, and 3X) on Day 0 had similar incidence of increased pigmented macrophages at the left ham injection sites (6 of 12 piglets; 1 of 10 piglets; 3 of 12 piglets; and 7 of 12 piglets, respectively). All the test article groups (1X, 2X, and 3X) treated on Day 7 had increased incidence of minimal pigmented macrophages at the right ham injection sites (2 of 10 piglets; 5 of 12 piglets; 9 of 12 piglets, respectively compared to the right ham (untreated) site of the controls (0 of 12 piglets). These findings were determined to be normal and expected after iron injections in piglets.

There were no effects on organ weights or organ-to-brain-weight ratio. Piglets on study gained weight as expected from birth to 14 days of age, and there were no differences in body weight of piglets across all treatment groups. None of the study piglets in any treatment group experienced clinical signs of iron toxicosis.

Conclusions: This study demonstrates the safety of iron hydrogenated dextran injection administered at 200 mg/mL at a dose of 200 mg/piglet used for the prevention or treatment of anemia due to iron deficiency in nursing piglets.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

Iron dextran is not an antimicrobial agent and is not known to have antibacterial activity; therefore, there was no requirement to assess this human food safety endpoint.

B. Toxicology and Residue Chemistry

In the FOI summary for NADA 138-255, dated April 8, 1985, the FDA determined that there is no human safety concern for residues resulting from the use of iron hydrogenated dextran injection at a dose of 100 mg/piglet under regulated conditions of use. Current understanding of iron's role in human health reinforces the conclusion that, even at a dose of 200 mg/piglet, there is no human food safety concern regarding residues.

It is not necessary to establish an acceptable daily intake (ADI) or tolerances for residues in edible tissues. A withdrawal period is not required.

C. Analytical Method for Residues

An analytical method for residue detection is not required.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to IRON DEXTRAN 20% INJECTION:

User Safety Warning: Not for use in humans. Keep out of reach of children. To obtain a Safety Data Sheet(s), contact Sparhawk Laboratories Inc at 1-800-255-6388 or at sparhawklabs.com.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that IRON DEXTRAN 20% INJECTION, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above. Additionally, data demonstrate that residues in food products derived from species treated with IRON DEXTRAN 20% INJECTION will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed over the counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

This supplemental approval for IRON DEXTRAN 20% INJECTION qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety studies. This exclusivity begins as of the date of our approval letter and only applies to the new strength (200 mg/mL) and dose (200 mg/piglet) that is approved in the supplemental application.

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval required a reevaluation of certain safety data in the application.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.