Safety Update Review:

See Medical Review dated

Sept. 12, 1997.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

CHEMISTRY REVIEW(S)

DIVISION OF MEDICAL-IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS, HFD-160

Review of Chemistry, Manufacturing, and Control

NDA#: 20-292 **CHEMISTRY REVIEW #:** 2 **REVIEW DATE:** 15-SEP-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AC	11-APR-97	14-APR-97	18-APR-97

NAME/ADDRESS OF APPLICANT: Oncomembrane, Inc.
1201 Third Avenue, Suite 3010
Seattle, WA 98101
(206) 622-6626/ Toshihiko Tanaka, President

DRUG PRODUCT NAME:

Proprietary:	FerriSeltz™
Nonproprietary/USAN:	Ferric ammonium citrate, brown
Code Name/Number:	CAS# 1185-57-5
Chem. Type/Therap. Class:	**3 S**

PHARMACOL.CATEG./INDICATION: DIAGNOSTIC-Imaging
T_1-weighted MRI contrast agent

DOSAGE FORM: Granular Powder for reconstitution into an effervescent solution

STRENGTHS: 600mg FAC, brown (105mg Fe) per 3g packet

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __X__Rx ____OTC

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL.WT.:

IUPAC: Iron (III) ammonium citrate CAS: Ammonium iron (III) citrate
Average stoichiometric formula:
Elemental formula: $C_{6.6}H_{12.8}FeN_{1.6}O_{9.7}$ as a polymeric coordination complex
Structure: Undetermined M.W.: Undetermined
Iron Content:

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS: US Patent #: 5,174,987--Dec 29, 1992
CONSULTS: NONE

CONCLUSIONS/RECOMMENDATIONS: **Approval Letter of FerriSeltz (600 mg) power packets in 20-count container size with revised expiration dating of 15 months.** CMC deficiencies identified in Chemistry review #1 were resolved satisfactorily by the firm, except for the need to revise expiry dating from 36 months to 15 months. AAI is the sole manufacturing and control site of FerriSeltz. The post-approval commitment to monitor the stability of the drug product have also been included and are satisfactory.

REMARKS/COMMENTS:

After this second Chemistry review the conclusion is to recommend approval of the NDA based on the resolution of the deficiencies identified in chemistry review #1.

Specifically the applicant has provided additional information to satisfy the following areas:

* reference standard for the drug substance, FAC, brown,
* adequate production data at AAI commercial manufacturing site,
* adequate update of MV package,
* adequate explanation and data to justify some of the proposed specifications,
* stability data in support of 15 months of expiration dating for FerriSeltz instead of the 36 months proposed in original NDA,
* EA information, "Categorical Exclusion" proposed,
* adequate post-approval commitment to monitor the stability of FerriSeltz, and
* acceptable cGMPs status: 16-Jul-97 for FerriSeltz production and testing.

RECOMMENDATION:

APPROVAL WITH 15 MONTHS EXPIRATION DATING FOR FERRISELTZ, 600mg, POWDER , 20-COUNT SIZE CONTAINER.

cc:
Orig. NDA # 20-292
HFD-160/Division File
HFD-160/MSalazar
HFD-160/SChow
HFD-160/DBailey
HFD-160/ELeutzinger
HFR-PA300/Seattle District Office
HFR-MA160/Philadelphia District Laboratory
HFC-134/Division of Field Investigations
HFD-161/KColangelo
R/D Init. by: ELeutzinger
F/T by: MSalazar

APPEARS THIS WAY
ON ORIGINAL

E. Leutzinger 9/24/97

15/Sep/97

Milagros Salazar-Driver, Ph.D.
Review Chemist, HFD-160
ONDC II, HFD-820

Filename: **N20-292.002**

SUMMARY OF CHEMISTRY REVIEW# 2

NDA 20-292
Ferriseltz (Ferric Ammonium Citrate, brown) 600mg
Oncomembrane, Inc.

A. DRUG SUBSTANCE

1. DESCRIPTION & CHARACTERIZATION: Satisfactory, Review#1, p 10.
2. MANUFACTURER: Satisfactory, Review#1, p 11.
3. SYNTHESIS: Satisfactory , Review#1, p 12.
4. **SPECIFICATIONS / TEST METHODS/REF.STD.: Satisfactory, Review#2, p 4**
5. CONTAINER/CLOSURE SYSTEM: Satisfactory, Review#1, p 17.
6. STABILITY: Satisfactory, Review#1, pp 18-19.

B. DRUG PRODUCT

1. COMPONENTS/COMPOSITION: Satisfactory, Review#1, pp 20-22.
2. SPECIFICATIONS & METHODS FOR INGREDIENTS: Satisfactory, Review#1, p 21 .
3. MANUFACTURER: Satisfactory, Review#1, p 22.
4. **MANUFACTURING AND PACKAGING: Satisfactory, Review#2, pp 5-6**
5. **SPECIFICATIONS AND TEST METHODS: Satisfactory, Review# 2, pp 7-11**
6. CONTAINER/CLOSURE SYSTEM: Satisfactory, Review#1, p 32.
7. **STABILITY: Satisfactory for 15 months expiration dating, Review#2, pp12-16**

C. INVESTIGATIONAL FORMULATIONS: Satisfactory, review#1, p 42.

D. ENVIRONMENTAL ASSESSMENT: Satisfactory. Addendum to Review#2 dated 24-Sep-97, Categorical Exclusion granted.

E. METHODS VALIDATION: In-progress. Adequate MV package for FDA Labs to review, Review#2, pp 17-22. MV request memo dated 11-Sep-97.

F. LABELING: Satisfactory, Review#2, p23

G. ESTABLISHMENT INSPECTION: cGMP status as of 16-Jul-97: ACCEPTABLE , Review#2, p25

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

APPROVAL OF THE FerriSeltz 20-COUNT SIZE CONTAINER WITH 15 MONTHS EXPIRATION DATING.

APPEARS THIS WAY
ON ORIGINAL

OCT 18 1996

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA#: 20-292 **CHEMISTRY REVIEW #:** 1 **REVIEW DATE:** 23-AUG-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-NOV-92	16-NOV-92	06-DEC-92
RESUBMISSION	15-NOV-95	16-NOV-95	28-NOV-95
NC	11-JAN-96	16-JAN-96	09-FEB-96
BZ	05-FEB-96	06-FEB-96	16-FEB-96
N (BC)	28-FEB-96	29-FEB-96	18-MAR-96
N (BC)	10-JUL-96	11-JUL-96	17-JUL-96

NAME/ADDRESS OF APPLICANT: Oncomembrane, Inc.
1201 Third Avenue, Suite 3010
Seattle, WA 98101
(206) 622-6626/ Toshihiko Tanaka, President

DRUG PRODUCT NAME:

Proprietary:	FerriSeltz™
Nonproprietary/USAN:	Ferric ammonium citrate, brown
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Chem. Type/Therap. Class:	**3 S**

PHARMACOL.CATEG./INDICATION: DIAGNOSTIC-Imaging
T_1-weighted MRI contrast agent

DOSAGE FORM: Granular Powder for reconstitution into an effervescent solution

STRENGTHS: 600mg FAC, brown (105mg Fe) per 3g packet

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __X__Rx ____OTC

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL.WT.:

IUPAC: Iron (III) ammonium citrate CAS: Ammonium iron (III) citrate
Average stoichiometric formula:
Elemental formula: $C_{6.6}H_{12.8}FeN_{1.6}O_{9.7}$ as a polymeric coordination complex
Structure: Undetermined M.W.: Undetermined
Iron Content:

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS: US Patent #: 5,174,987--Dec 29, 1992
CONSULTS: NONE

CONCLUSIONS/RECOMMENDATIONS: Non Approval Letter. CMC deficiencies include lack of reference standard for the drug substance, FAC, brown. Inadequate production data and stability studies in support of the expiration dating for FerriSeltz intended for marketing, as well an inadequate justification for proposed specs, EA report and post-approval commitment to monitor the stability of the drug product.

REMARKS/COMMENTS:

Background

Ferric Ammonium citrate (FAC) has been used in about 25 OTC products (oral solutions), 4 prescription products in the past as hematinic nutrient or dietary supplement. Most of these OTC products were withdrawn during 1970 and 1971 (DESI initiative), while the prescription ones are reported with No Action status.

Geritol Liquid/oral, iron as FAC, 50 mg/15mL (Beecham Products), and Geriplex-FS Liquid/oral, iron (as FAC, green), 15mg/30mL are OTC products currently in the market containing ferric ammonium citrate.

Recommendation at the 45 DAY file meeting: to file NDA after the applicant agreed to withdraw proposed manufacturer of drug product, Applied Analytical Industries, Inc., since this site has not produced the product at this site, nor has generated stability data in support of AAI site. (Communication of 11-Jan-96 NC).

The proposed manufacturing site for FerriSeltz effervescent powder will be Pharmavite, Inc. which was the site originally proposed for the NDA and the one manufacturing all stability and production size batches presented in this NDA.

In the 5-Feb-96 BZ communication the applicant responded to preclinical, clinical, and CMC comments raised during the filing of the application.

On 28-Feb-96 N(BC) amendment the applicant informed the Agency of a decision in which was no longer to be the manufacturer of FerriSeltz and their inability to manufacture the product since part of the production equipment had been transferred to AAI. Therefore, the company proposed AAI again as the commercial production site; however, they would not be ready for inspection until mid-July.

Amendment of 10-Jul-96 N(AC), provides the information on the transfer of analytical methodology to AAI as well as stability data for 3 lots manufactured at AAI including their production batch records.

After this first comprehensive Chemistry review the conclusion is to withhold approval of the NDA based on major deficiencies which include the following areas:

* include lack of reference standard for the drug substance, FAC, brown,
* inadequate production data,
* applicant withdrawal of readiness for inspection after 45 day filing commitments,
* Inadequate explanation and data to justify some of the proposed specifications,
* inadequate stability studies in support of the expiration dating for FerriSeltz intended for marketing,
* inadequate EA report, and
* inadequate post-approval commitment to monitor the stability of FerriSeltz.

RECOMMENDATION: NON APPROVAL LETTER

cc:
Orig. NDA # 20-292
HFD-160/Division File
HFD-160/MSalazar
HFD-160/SChow
HFD-160/DBailey
HFD-160/ELeutzinger
HFR----------PA300/Seattle District Office
HFR----------MA160/Philadelphia District Laboratory
HFC-134/----------Division of Field Investigations
HFD-161/Cusack
R/D Init. by: ELeutzinger
F/T by: MSalazar

E. Leutzinger 10/15/96

23-Aug-96

Milagros Salazar-Driver, Ph.D.
Review Chemist, HFD-160
ONDC II, HFD-820

Filename: **N20-292.001**

APPEARS THIS WAY
ON ORIGINAL

Consult #597 (HFD-160)

FERRISELTZ ferric ammonium citrate, brown for oral administration

The LNC found no look alike/sound alike conflicts nor misleading aspects in the proprietary name.

The Committee believes the correct established name for the product should be effervescent ferric ammonium citrate, brown, for oral solution to be in conformance with the USP oral solution categories.

The LNC has no reason to find the proposed proprietary name unacceptable.

D L Boring 5/23/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

cc
orig NDA 20-292
DJJ file

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

* * * SENSITIVE * * *

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-292

FerriSeltz (Ferric ammonium citrate, brown) Effervescent Powder

Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

CENTER FOR DRUG EVALUATION AND RESEARCH

First Review
DATE COMPLETED 7/10/96

ENVIRONMENTAL ASSESSMENT

NDA 20-292 FerriSeltz, Ferric ammonium citrate, brown (FAC, brown) Granular Powder.

This is the first review of the environmental assessment (EA) submitted under 21 CFR 25.31a(a). During a pre-NDA meeting, 21-Feb-95, the company was advised by the Agency to provide a full environmental assessment in the NDA. During the 45 day NDA file meeting, 3-Jan-96, the EA section was considered to be fileable for review.

Items 1, 2, 3:
Submission is dated July 1, 1994. Name of Applicant, Oncomembrane, Inc., and address are included. Adequate

Item 4:
a), b)
The drug is FerriSeltz (Ferric ammonium citrate, brown, FAC) Granular Powder. Each packet contains 3 g of dry powder which has
The indication is for use as diagnostic Magnetic Resonance Imaging (MRI) enhancement agent.

EA submitted using a document format arranged under 21 CFR 25.31a(a).

c), d), e)
The location of manufacture and site description for the manufacturer of the Drug substance (FAC, brown) and the drug product (FerriSeltz) are adequate.

Drug substance:

Drug Product: Applied Analytical Industries, Inc. (AAI)
1206 North 23rd St.
Wilmington, NC 28405

The drug will be used by physicians at health care facilities. Disposal is discussed later.

Item 5
Identification of the drug substance 's molecular formula, weight, structure discussion is included. A material Safety Data Sheet for FAC, brown is included in

Appendix A of the NDA/EA section. The list of reagents used in the manufacture of the FAC. Brown drug substance is not presented as part of EA. However, this information is presented in a CMC Section 2. II. 1. And in the DMF# 9603. Identification of all components of the drug product are included in Appendix B of the NDA/EA section.

Adequate

Item 6
a), b)
For Drug Substance-- manufacturer The applicant states that the emissions from the facility are in compliance with the government environmental laws according with appropriate laws and regulations.

For Drug Product-- manufactured in North Carolina. Applicant states that manufacturer complies with federal and state regulations.

Air emissions-- discussion adequate.

Water emissions/Wastewater-- discussion adequate. Waste waters discharged through sewer system.

c) Compliance
For drug substance-- Appendix C of NDA/EA section contains EA from facility from with signature of responsible official. Appendix D of NDA/EA section contains letters of compliance certified by the Prefectural government of Adequate

For drug product-- Applicant states that AAI facility with federal and state laws as per Clean air Act, and Federal Water Pollution Control Act of 1972, the clean Water Act, and the Water Quality Act of 1987. Waste discharge being in compliance as per 40 CFR 439. Solid waste-- AAI is registered as a hazardous waste generator. According to
Other compliance status include chemicals stored and handled and managed according to GMPs and OSHA standards. Adequate

d), e) Expected Introduction Concentrations
Estimated 5th year production volume information is included in Appendix F of the NDA/EA section. Calculation in item 6 states the MEEC, based on 5-yr production data, is Adequate

Deficiency: The applicant needs to described how the rejected lots and returned lots of the product will be disposed of.

Item 7:
FAC, brown is very soluble in water, but insoluble in alcohol. Therefore, the compound is to enter the aquatic compartment as the parent compound and reside as this form in that environment.
Estimated biodegradability for FAC, brown in an aerobic medium, at dark at temperature o 22 ± 3°C, and concentration of Mineralization (CO_2 production) degradation was The Microbial inoculum was activated sludge an secondary effluent from Columbia wastewater Treatment Plant. The theoretical value for FAC, brown was against a reference substance (dextrose) with a mineralization (CO_2 production) value of A report of this testing is presented with test results and summary discussion in Appendix G.

Test substance, FAC, Brown, Lot#: D1262018 provided by

Reference Substance: Dextrose, ACS grade
Appendix G--Vol 2.03, 030001 presents the results of study on Aerobic Biodegradation in water of FAC, brown. The study was performed by:

Compliance Certification by environmental officers (with names/titles and signatures) in the company is presented too.
ADEQUATE

Item 8:
Microbial Inhibition test with FAC, brown, on microbes in the environment as EC_{50} was estimated to be but was not calculated because the highest concentration tested did not cause 50% or greater inhibition. The maximum inhibition was . Microbial inoculum: activated sludge from Columbia Waste treatment Plant/Columbia, MO (this plant received domestic sewage).
Test substance : FAC, Brown, Lot# D12620/provided by

Reference Substance:

A report of this testing, with results,calculations, and a summary discussion, is presented in Appendix H.

Appendix H--Vol 2.03, 030370 presents the results of study on Activated Sludge Respiration Inhibition Test with FAC, BROWN. The study was performed by:

Compliance Certification by environmental officers (with names/titles and signatures) in the company is presented too. No potential effect on microbial environment is expected.
ADEQUATE

Item 9, 10, and 11:
Meets requirements. Adequate

REVIEWER'S NOTES:
Items 7 through 11 are not needed because the application meets requirements for abbreviated AEA, both for infrequent use and according to Tier 0 approach, i.e. < 1 ppb.

Item 12:
Preparer is stated by name as Nancy Grice McGowan.
Deficient

Deficiency: Job Title and qualifications (e.g., educational degrees) of the preparer should be presented, contract testing laboratories, and agencies consulted should be identified.

Item 13:
Certification is given by the President of the Company. Adequate.

Appendices are given for MSDS for FAC, brown (drug substance) not for FerriSeltz powder packets (drug product), Composition of FerriSeltz powder 3g packets, Compliance certification for production of drug substance, Compliance certification for production of drug product, 5-year production proforma. Adequate

Deficiencies: A dated, signed certification should be signed by the responsible official, and the following statement should be included in item 13:

1. "The undersigned official certifies that the EA summary document (pages x-x) and Appendices x-x (pagesx-x) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6."

Item 14, & 15:
Adequate information.

CONCLUSION:
There is adequate information contained here for a full or Tier 0 EA abbreviated format, except for the deficiencies stated in the review. The MEEC is than 1ppb. The applicant needs to be informed of the deficiencies. All permits, including those for the foreign facility, appear to be accounted for and cited. No likely significant adverse environmental effects are determined from the review of this EA. A FONSI is recommended.
Draft comments attached.

Prepared by _____ 7/10/96
Milagros Salazar, Ph.D. Review Chemist, HFD-160 Date

cc:
HFD-160/ orig NDA
HFD-160/Div file
HFD-160/Leutzinger/Salazar
HFD-160/Cuzack
HFD-357/file NDA 20-292
HFD-357/Sager

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: 18 November 1996
To: File NDA 20-292 (FerriSeltz)
From: Laraine L. Meyers, PhD, RPh

Subjects: 1. Genetic toxicity studies
2. Acute i.p. study

---

1. This NDA does not include genetic toxicity studies which currently are generally required for characterization of the safety profile of a marketed drug. At the time of IND and NDA submissions for FerriSeltz (orally administered), genetic toxicity studies were not requested, most likely because iron salts have been extensively utilized as OTC oral hematinics for many years and because the other NF and USP ingredients are also commonly used in OTC preparations and/or food. I agree that the lack of genotoxicity studies is not a critical deficiency in the NDA. I suggest that the labeling section on carcinogenesis/mutagenicity simply state that studies for genotoxic potential were not performed.

2. An acute intraperitoneal toxicity study in rats was performed in compliance with GLPs at . in 1991. The purpose was to investigate potential toxicity of FerriSeltz in the event of leakage into the peritoneum via a gut perforation. An intraperitoneal study is required routinely for orally administered contrast agents used for imaging the gastrointestinal tract.

The study did not reveal adverse effects during the 14-day observation period following a single dose of 120 mg/kg (1/2 the maximum recommended dosage of 12 grams based upon body weight for a 50 kg patient). It is important to note that according to the study protocol, only gross lesions were to be examined histologically. Since no lesions were noted at necropsy, no abdominal tissues were examined for microscopic lesions. This is a protocol deficiency; abdominal tissues should be evaluated for potential histopathology such as inflammatory response which may lead to adhesions regardless of whether there are macroscopic findings.

For the use of FerriSeltz in the indicated populations for the present NDA, the lack of histologic examination of abdominal tissues is considered not to be a critical deficiency. However, if patients with GI perforations/fissures or prolonged GI transit time are studied in the future, or if clinical use otherwise places patients at risk of peritoneal exposure, a more complete intraperitoneal study to include histologic examination of exposed tissues should be conducted with exaggerated doses in an appropriate animal model.

Laraine L. Meyers 18 Nov 1996
Laraine L. Meyers, PhD,RPh / Date

cc: Achiv NDA 20-292
HFD-160 Div file NDA 20-292
HFD-160//Love/Raczkowski/Jones/Chow

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 20-292 RS

Ronald L. Dundore, Ph.D.
Reviewing Pharmacologist

DOCUMENT NUMBER: NDA 20-292 RS
SUBMISSION DATE: November 15, 1995
CENTER RECEIPT DATE: November 16, 1995
REVIEWER RECEIPT DATE: March 27, 1996
DRAFT REVIEW COMPLETE: July 10, 1996

SPONSOR: Oncomembrane, Inc.
1201 Third Ave., Suite 3010
Seattle, WA 98101

DRUG: FerriSeltz™, ferric ammonium citrate, OMR

PROPOSED INDICATION: Oral contrast agent for magnetic resonance imaging of the upper abdomen.

FORMULATION: Each 3 gram packet of FerriSeltz™ contains the following:

Ingredient	Amount
Ferric ammonium citrate, brown, USP	600 mg
(as elemental iron)	105 mg
Sodium bicarbonate, USP	1250 mg
Tartaric acid, NF	1100 mg
Aspartame, NF	47 mg
Grape flavoring, Micron ZD-3870	3 mg

PROPOSED DOSING REGIMEN: FerriSeltz™ is administered orally to patients who have fasted for a minimum of 6 hr. The recommended dose of FerriSeltz™ is 2-4 packets dissolved in 600 ml of water. Therefore, the proposed human dose is 6-12 g or 120-240 mg/kg of FerriSeltz™ (assuming a 50 kg human). The human dose of FerriSeltz™ also represents 210-420 mg Fe or 4-8 mg Fe/kg.

RELATED NDA/IND:

BACKGROUND INFORMATION: The original NDA was submitted on 11/12/92 but was not filed (refusal to file letter dated 1/8/93); no pharmacology/toxicology issues were included in the refusal to file letter. The NDA was resubmitted on 11/16/95. The active ingredient in FerriSeltz™, ferric ammonium citrate (FAC), is the active ingredient in a number of OTC products including Geritol® Liquid. FAC has been granted Generally Recognized as Safe (GRAS) status as a nutrient supplement with no limitations other than good manufacturing practice (53 FR 16862). A number of the studies included in the application were submitted

previously to support and, as such, were reviewed by Dr. A. Weir . A portion of this review was excerpted from the previous review

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

No nonclinical ADME studies were included in the application.

ACUTE TOXICITY

1. Acute oral toxicity study of ferric ammonium citrate in rats. Study no. 005852, conducted by Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan, in-life phase 9/12/89-11/22/89, report dated 2/13/90, in compliance with Japanese Good Laboratory Practice standards.

Methods: Sprague-Dawley rats, 5/sex/group, received an oral dose of distilled water or 2000 mg/kg FAC (amount of Fe not provided). The dose volume for both groups was 10 ml/kg. The rats were maintained for 14 days after dosing. Toxicity was assessed by clinical observations (1, 2, 4, 6, and 8 hr after dosing and daily thereafter), body weight (pretest and on days 1, 3, 7, 10 and 14), food consumption (weekly) and necropsy.

Results: Diarrhea and perianal staining were observed on the day of treatment. On days 1 and 2, black feces were observed. No other effects were noted.

2. An acute oral toxicity study of OMR formulation in the rat. Study no. 5859-90, conducted by in-life phase 6/21/90-7/5/90, report dated 1/3/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Sprague-Dawley rats, 5/sex/group, received an oral dose of distilled water or 120, 1200 or 2000 mg/kg of FerriSeltz™ (4, 40 or 67 mg Fe/kg). The dose volume for all groups was 10 ml/kg. The rats were maintained for 14 days after dosing. Toxicity was assessed by clinical observations (daily checks for clinical signs and twice daily checks for mortality), body weight (pretest and on days 3, 7, 10 and 14), food consumption (weekly), gross pathology, organ weight (absolute and relative) and histopathology of all relevant tissues.

Results: Soft stools and/or fecal staining in several mid and high dose (1200 and 2000 mg/kg) animals at 2 and/or 4 hr after dosing were the only treatment-related findings in this study.

Reviewer comments: Due to the relatively insignificant nature of the treatment-related effects, 2000 mg/kg is considered the no observed effect level (NOEL) for this study. The

softened stool and fecal staining were not observed in the repeat dose study in which rats received 40, 120, 360 or 1200 mg/kg/day of FerriSeltz™ for 14 days. This difference may be due to the rats in the repeat dose study not being fasted prior to treatment.

3. An acute intraperitoneal toxicity study of OMR formulation in the rat. Study no. 5858-90, conducted by in-life phase 6/20/90-7/10/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Sprague-Dawley rats, 5/sex/group, received a 10 ml/kg i.p. injection of saline or a 120 mg/kg i.p. injection of FerriSeltz™. The animals were maintained for 14 days after treatment. Toxicity was assessed by clinical observations (daily monitoring for clinical signs and twice daily mortality checks), body weight (pretest and on days 3, 7, 10 and 14), food consumption (twice weekly), clinical pathology (hematology, coagulation studies, clinical chemistry and urinalysis), gross pathology and histopathology of gross lesions.

Results: No adverse effects were reported.

4. An acute oral toxicity study of OMR formulation in the dog. Study no. 90-3577, conducted by in-life phase 7/6/90-7/22/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Beagle dogs, 3/sex/group, received an oral dose of distilled water of 120, 1200 or 2000 mg/kg of FerriSeltz™ (4, 40 and 67 mg Fe/kg). The dose volume for all groups was 10 ml/kg. The dogs were maintained for 14-16 days after dosing. Toxicity was assessed by observations for mortality and clinical signs (1, 2, and 4 hr after dosing and daily thereafter), body weight (pretest, days 3, 4, 7, 11 and 14 and prior to necropsy), food consumption (weekly), gross pathology, organ weight (absolute and relative) and histopathology of all relevant tissues (control and high dose dogs only except for the testes and epididymides in which case all groups were examined).

Clinical observations: Emesis shortly after dosing in all high dose males and watery stools for 1 or 2 days after dosing in all mid and high dose dogs were associated with treatment.

Body weight and food consumption: Body weight gain for females in the 2000 mg/kg dose group was significantly decreased relative to controls at 3, 4 and 7 days after treatment. Although food consumption was decreased during week 1 for these animals, the difference was not statistically significant.

Gross pathology: No effects were observed.

Organ weight: In dogs receiving 1200 and 2000 mg/kg, mean testes weight (absolute and relative to body and brain weights) were decreased approximately 40% relative to the control value. The testes/body weight ratio was significantly decreased in both treatment groups. This effect may be related to variations in the stage of sexual maturity.

Histopathology: No effects were observed. The reproductive organs were characteristic of young sexually immature dogs.

Reviewer comment: Since neither the weight loss nor the testicular effect observed in this study were observed in the repeat dose dog study described below, these effects are not considered treatment-related. The NOEL is considered to be 2000 mg FerriSeltz™/kg.

REPEAT DOSE TOXICITY

1. A 14-day subacute oral toxicity study of OMR formulation in the rat. Study no. 90-3604, conducted by in-life phase 9/17/90-10/8/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Sprague-Dawley rats received an oral dose of distilled water or 40, 120, 360 or 1200 mg/kg/day of FerriSeltz™ (5 times the maximum human dose) for 14 days. The groups receiving 40, 120 and 360 mg/kg/day contained 10 rats/sex/group; the control and 1200 mg/kg/day groups contained 15 rats/sex/group. All dose volumes were 10 ml/kg. One or two days after the last dose was given, 10 rats/sex/group were sacrificed. The remaining 5 rats/sex/group in the control and 1200 mg/kg groups were sacrificed after a 7 day recovery period. Toxicity was assessed by observations for mortality and clinical signs (twice daily), physical examination (pretest and daily), ophthalmoscopic examination, body weight (pretest and twice weekly thereafter), food consumption (pretest and twice weekly thereafter), clinical pathology (clinical chemistry, hematology and urinalysis), necropsy, organ weight (absolute and relative) and histopathology of relevant tissues (for the control and high dose groups only).

Results: No effects clearly attributable to FerriSeltz™ were evident.

Reviewer comment: The NOEL for this study is considered to be 1200 mg FerriSeltz™/kg/day.

2. Dosage-range repeated administration toxicity study of OMR formulation administered orally via stomach tube to nonpregnant New Zealand white rabbits. Study no. 215-003, conducted by in-life phase 9/9/91-9/23/91, report dated 1/3/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Female rabbits (n=5/group) were given distilled water (10 ml/kg) or 120, 360, 1200 or 2000 mg/kg/day of FerriSeltz™ orally by gavage daily for 14 days. The animals were observed daily for clinical signs of toxicity, body weight and food consumption. After the 14 day observation period, the animals were sacrificed and subjected to necropsy.

Results: One animal given 120 mg/kg/day of the test agent died as a result of a intubation accident. No other deaths were observed. The daily administration of FerriSeltz™ at doses as high as 2000 mg/kg/day did not produce biologically relevant changes in body weight, body weight gain or food consumption. The gross pathological examinations were unremarkable.

3. A 14-day subacute oral toxicity study of OMR formulation in the dog. Study no. 90-3578, conducted by in-life phase 9/21/90-10/9/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Beagle dogs, 3/sex/group, received an oral dose of distilled water or 40, 120, 360 or 1200 mg/kg (5 times the maximum human dose) of FerriSeltz™ per day for at least 2 weeks. All dose volumes were 10 ml/kg. The dogs were sacrificed 1 day after receiving the final dose. Toxicity was assessed by observation for mortality and clinical signs (twice daily), testes measurements (prior to dose and on days 1 and 7 and prior to sacrifice), ophthalmoscopic examination, body weight (pretest and twice weekly thereafter), food consumption (pretest and twice weekly thereafter), clinical pathology (clinical chemistry, hematology and urinalysis), necropsy, organ weight (absolute and relative) and histopathology of relevant tissues (for the control and high dose groups only).

Results: Abnormalities attributed to FerriSeltz™ were limited to a marked increase in the incidence of watery stools in dogs receiving 360 and 1200 mg/kg/day. No other effects clearly attributable to FerriSeltz™ were evident.

Reviewer comment: Based on the increased incidence of watery stools, the NOEL was considered to be 120 mg/kg/day.

REPRODUCTIVE TOXICITY

1. Dosage-range developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via gavage to Crl:CDBR VAF/Plus presumed pregnant rats (including skeletal and soft tissue evaluation of two dosage groups). Study no. 215-003P, conducted by in-life phase 9/3/91-9/26/91, report dated 1/23/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Eight presumed pregnant rats were randomly assigned to each of 4 treatment groups and received distilled water (10 ml) or 120, 360 or 1200 mg/kg/day of FerriSeltz™ orally by gavage on days 6 through 15 of gestation. The rats were observed daily for signs of toxicity, abortion, premature deliveries, body weight and food consumption. Rats were sacrificed on day 20 of presumed gestation. A gross necropsy of the thoracic and abdominal viscera was performed. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. The number of corpora lutea in each ovary was recorded. Each fetus was weighed and examined for gross external alterations. Approximately one-half of the fetuses in the control and high dose groups were examined for soft tissue alterations. The remaining fetuses in each litter were examined for skeletal alterations.

Maternal observations: No deaths, abortion or premature deliveries were caused by treatment. The average maternal body weight gain was significantly decreased by 20% during days 6 to 20 of gestation in the 1200 mg/kg/day dose group when compared to controls. Food consumption was also decreased in these animals. No other signs of toxicity were observed.

Fetal observations: The administration of the test agent had no effects on the numbers of corpora lutea, resorptions or live and dead fetuses. The fetal sex ratio and body weights were not affected by treatment. Two fetuses from the 1200 mg/kg/day dose group exhibited depressed eye bulges; one of the fetuses exhibited microphthalmia of the right eye and one exhibited small eye sockets and a bifid centrum of the 9th thoracic vertebra. Although these alterations are occasionally noted in control animals in this laboratory, a relationship to treatment could not be ruled out since the alterations were observed in the high dose group only in this study.

Reviewer comment: Since the decreases in maternal body weight gain and the fetal abnormalities observed in this pilot study were not observed in the definitive study described below, a relationship to treatment seems unlikely.

2. Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via gavage to Crl:CDBR VAF/Plus presumed pregnant rats. Study no. 215-003, conducted by in-life phase 11/5/91-11/27/91, report dated 3/20/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Twenty-five presumed pregnant rats were randomly assigned to receive distilled water (10 ml/kg) or 120, 360 or 1200 mg/kg of FerriSeltz™ orally be gavage on days 6 through 15 of gestation. The rats were examined daily during the dosage and postdosage periods for clinical observations, abortion, premature deliveries and mortality. Body weights and food consumption were determined on day 0 and days 6 through 20 of gestation. On day 20 of gestation, all rats were sacrificed and subjected to necropsy. The

numbers and distribution of implantations, early and late resorptions, live and dead fetuses and corpora lutea were determined. Each fetus was weighed and examined for sex and gross external alterations. Approximately one-half of the fetuses were examined for soft tissue alterations. The remaining fetuses were examined for skeletal alterations.

Maternal observations: The administration of FerriSeltz™ produced no obvious signs of maternal toxicity. Maternal body weight gain and food consumption were not affected by treatment.

Fetal observations: The numbers of corpora lutea, implantations, resorptions and live and dead fetuses were not affected by treatment with FerriSeltz™. The fetal sex ratio and body weights were also unaffected by treatment. The visceral and skeletal abnormalities observed in the litters of treated dams occurred at incidences not statistically different from those of the control group.

3. Dosage-range developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via stomach tube to New Zealand white rabbits (including soft tissue and skeletal evaluation of two dosage groups). Study no. 215-002P, conducted by in-life phase 10/30/91-11/28/91, report dated 4/13/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Inseminated rabbits (5/group) received distilled water (10 ml/kg) or 360, 1200 or 2000 mg/kg/day of FerriSeltz™ orally on days 6 through 18 of gestation. The rabbits were examined daily for signs of toxicity. Body weights were recorded twice before dosing and on days 0 and 6 through 29 of gestation. Food consumption was measured on days 0 through 29 of gestation. On day 29 of gestation, rabbits were sacrificed and subjected to gross necropsy of the thoracic and abdominal viscera. The uterus from each rabbit was excised and examined for pregnancy, number and distributions of implantations, live and dead fetuses and early and late resorptions. The number of corpora lutea in each ovary was recorded. Each fetus was examined for sex and gross external alterations. The fetuses from the control and high dose groups were examined for visceral and skeletal alterations.

Maternal observations: No rabbits died, aborted or delivered prematurely. No signs of toxicity were noted. Body weight and food consumption were not affected by treatment.

Fetal observations: The numbers of corpora lutea, implantations and live fetuses were not different among the treatment groups. The percentage of resorbed conceptuses per litter tended to increase in a dose-related manner. However, the percentages of resorbed conceptuses were not statistically different among the treatment groups and were within the historical laboratory control limits. Fetal weight was unaffected by treatment. The examination of the fetuses from the control and high dose groups revealed no visceral or

skeletal alterations due to treatment.

4. Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via stomach tube to New Zealand white rabbits. Study no. 215-002, conducted by in-life phase 2/10/92-3/13/92, report dated 7/17/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Inseminated rabbits (20/group) were given distilled water (10 ml/kg) or 360, 1200 or 2000 mg/kg/day of FerriSeltz™ orally on days 6 through 18 of gestation. The rabbits were examined daily for signs of toxicity, abortions and premature deliveries. Body weights were measured on days 0 and 6 through 29 of gestation. Food consumption was measured daily on days 0 through 29 of gestation. On day 29 of gestation, the rabbits were sacrificed and subjected to gross necropsy of the thoracic and abdominal viscera. The uterus was excised and examined for the number and distribution of implantations, early and late resorptions and live and dead fetuses. The number of corpora lutea in each ovary was recorded. Each fetus was weighed and examined for sex and visceral alterations. The fetuses were eviscerated and examined for skeletal alterations.

Maternal observations: No deaths occurred during the conduct of the study. Two animals (one in the control group and one in the mid dose group) aborted spontaneously. Four of the animals in the high dose group exhibited abnormal feces (soft or liquid feces, dried feces or no feces). No other clinical observations related to treatment were noted. The treatment with FerriSeltz™ had no obvious effect on body weight, body weight gain or food consumption.

Fetal observations: The numbers of corpora lutea, implantations, live fetuses and early and late resorptions were similar among the groups. Treatment with the test agent had no effect on fetal body weight. Treatment with FerriSeltz™ had no statistically significant, dose-related effects on the incidence of visceral or skeletal alterations in the fetuses.

GENETIC TOXICITY

At the time the sponsor submitted the IND for FerriSeltz™ genetic toxicity studies were not given the critical status currently given to these studies. Due to the GRAS status of FAC and its use in OTC products and as a food additive, genetic toxicity studies were not requested when the IND and the original NDA for FerriSeltz™ were submitted.

SUMMARY AND EVALUATION

FerriSeltz™ is a preparation of ferric ammonium citrate (FAC) which is intended for use as an oral contrast agent in magnetic resonance imaging of the upper abdomen. FAC, the active ingredient in FerriSeltz™, is the active ingredient in a number of OTC products including Geritol® Liquid and has been granted Generally Recognized as Safe (GRAS) status as a nutrient supplement with no limitations other than good manufacturing practice (53 FR 16862). The proposed human dose of FerriSeltz™ is 6-12 g or 120-240 mg/kg (assuming a 50 kg human). This dose of FerriSeltz™ also represents 210-420 mg Fe or 4-8 mg Fe/kg.

The acute administration of FerriSeltz™ to rats and dogs at oral doses up to 2000 mg/kg (approximately 8 times the maximum human dose on a mg/kg basis) produced no obvious signs of toxicity other than a change in stools (soft or watery stools). No obvious toxic effects were noted after the acute intraperitoneal administration of 120 mg/kg of FerriSeltz™ (approximately one-half of the maximum human oral dose) in rats. The lack of overt toxicity after the intraperitoneal administration of the test agent suggests that the toxicological consequences of leakage into the peritoneum from a perforation in the GI tract after oral administration are minimal. The draft labeling states, however, that FerriSeltz™ is contraindicated in patients with known or suspected complete bowel obstruction or perforation of the bowel.

The repeated (14-day) oral administration of FerriSeltz™ to rats and rabbits at doses up to 1200 mg/kg (5 times the maximum human dose) and 2000 mg/kg (8 times the maximum human dose), respectively, produced no obvious toxicity. Watery stools appeared to be the only negative effect produced by the repeated (14-day) administration of FerriSeltz™ to dogs at doses up to 1200 mg/kg. When administered repeatedly to pregnant rats and rabbits at doses of 1200 mg/kg and 2000 mg/kg, respectively, during the period of organogenesis (days 6 through 15 or 18 of gestation), FerriSeltz™ produced no obvious signs of maternal toxicity, embryo-fetal toxicity or teratogenic potential.

The sponsor did not provide rationale for the maximum doses of FerriSeltz™ used in the toxicity studies. The maximum doses used in the toxicity studies represented approximately 5-8 times the maximum human clinical dose on a mg/kg basis. FerriSeltz™ is intended for use as an acutely administered (single dose) diagnostic agent. FAC, the active ingredient in FerriSeltz™, has been granted GRAS status and is used in OTC products and as a food additive. Because no significant toxicity was observed after the repeated administration of FerriSeltz™, a preparation of the GRAS substance FAC, at doses representing 5-8 times the human clinical dose, the toxicity studies included in the application appear to support the safe use of FerriSeltz™ for the proposed indication.

Genetic toxicity studies were not requested from the sponsor during the development of FerriSeltz™ and, consequently, were not included in the application. Given the intended use

for FerriSeltz™ (acute administration as a diagnostic agent) and the GRAS status of FAC, the lack of genetic toxicity studies does not pose a significant safety concern.

LABELING

No changes in the draft labeling are suggested.

RECOMMENDATION

Approval of FerriSeltz™ as an oral contrast agent for magnetic resonance imaging of the upper abdomen is recommended.

Ronald L. Dundore, Ph.D.
Reviewing Pharmacologist

7/18/96
Date

I concur with conclusions and recommendation.
Lauren A. Meyers 7-18-96

cc: Orig NDA
HFD-160/Div File
HFD-160/MO/Chow
HFD-160/PharmTL/Meyers
HFD-160/Chem/Salazar
HFD-160/CSO/Cusack
HFD-345
HFD-427/Biopharm/Udo
HFD-713/Stat/Davi

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

CHEMISTRY REVIEW

To: NDA 20-292, FerriSeltz (ferric ammonium citrate, brown) 600mg

From: Milagros Salazar-Driver, Ph.D., HFD-160 MSD.

9/25/97

Subject: ADDENDUM TO REVIEW #2--
Environmental Assessment (EA): Categorical Exclusion Request

Date: September 24, 1997

The applicant's submission dated 19 September 1997 requests a Categorical Exclusion under 21 CFR 25.31(b) for the EA of this application according to the new EA regulations of July 1997.

The basis for the request is that the expected concentration entering into the aquatic environment has been calculated to be that 1 ppb using the FDA guidance for Industry for the submissions of EA in human drug applications and supplements (Nov. 1995).

The submission describes that assuming all drug substance produced and evenly distributed though the U.S. per day, and no metabolism, the environmental introduction concentration (EIC) is calculated to be as follows:

EIC-Aquatic (ppm) = AxBxCxD =

where: A = kg/year production =
B = l/liters per day entering POTWs =
C = year/365days
D =

Comments: This application would qualify for Categorical Exclusion according to the new regulation criteria under the following type of action for the following:

1. NDA does not result in increase use of an active moiety since it consists of a different formulation and dosage form of some already in the environment; and

2. The calculated EIC is 1ppb.

Categorical exclusion is granted under 21CFR 25.31(b).
ADEQUATE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

STATISTICAL REVIEW(S)

OCT 3 1996

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-292
SPONSOR:	Oncomembrane, Inc.
DRUG:	FerriSeltz (ferric ammonium citrate, brown)
INDICATION:	Upper abdominal imaging agent (T1 images only)
DOCUMENTS REVIEWED:	Volumes 2.01, 2.29 to 2.39, and 2.45 to 2.48 of the sponsor's NDA resubmission dated 11/15/95

DATE: Date received by Medical Division (Stamp Date): 11/16/95
Date received by Division of Biometrics: 11/22/95

MEDICAL REVIEWER:	S. Chow, M.D.
STATISTICAL REVIEWER:	R. Davi, M.S.

MAJOR REVIEW ISSUES:

- Although many of the primary efficacy parameters showed a highly statistically significant improvement for the post-dose images compared to the pre-dose images, other secondary parameters showed that the post-dose images were statistically inferior to the pre-dose images.
- In some cases, the pre-dose study image was used to develop the "gold standard diagnosis". This may have caused the pre-dose image diagnosis to agree with the "gold standard diagnosis" more often than was appropriate.
- The site investigators' evaluation of the images were unblinded with respect to dose and were based on viewing pre-contrast and post-contrast images side by side. The evaluations were also based on a scale which did not allow for the possibility of the post-dose image being worse than the pre-dose image.

I. Introduction

The sponsor has resubmitted the results of two open label, multi center, baseline-controlled phase 3 clinical trials designed to show that FerriSeltz is safe and efficacious as an oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T1 weighted magnetic resonance imaging (MRI) of the upper abdomen (filing meeting 1/4/93, no major statistical issues were cited as reasons for refusal to file). Studies A and B involved six centers each (no center participated in both studies). Two doses, 200 mg Fe/600 mL (6 g FerriSeltz) and 400 mg Fe/600 mL (12 g FerriSeltz), were evaluated in these trials. This submission also includes the results of a retrospective assessment of the images from these trials. The objective in re-evaluating these images was to gain an assessment of the clinical utility of FerriSeltz as was requested by FDA.

II. Study Design

Two hundred seventy five patients who were scheduled to undergo abdominal MRI

studies due to suspected or known diseases were enrolled in these trials (160 in Study A and 115 in Study B). Subjects were required to be able and willing to tolerate a six hour fast and to give their written informed consent. Patients who met any of the following exclusion criteria were not enrolled in the trial: less than 18 years of age; pregnant or nursing a child; "MRI exclusions" (e.g. pacemakers, surgical clips, or metallic implants, or claustrophobia); history of allergy or sensitivity to iron; history of hyperferremia, memochromatosis, or hemosiderosis; high grade intestinal tract obstruction; phenylketonuria; medical condition, presentation (vital signs), or medical history which may prevent safe participation in this study; received treatment with an investigational drug within the past 30 days; treatment with enteric agent or contrast agent within 24 hours prior to FerriSeltz; and treatment with glucagon, scopolamine, or other anti-peristaltic agent within 24 hours prior to FerriSeltz and concomitant with study MRI.

Subjects were randomized to receive a single dose of either 200 mg Fe/600 mL (6 g FerriSeltz) or 400 mg Fe/600 mL (12 g FerriSeltz). T1-weighted spin-echo MRI of the upper abdomen was performed before and 15 minutes after ingestion of FerriSeltz. All MRI variables were consistent for the pre- and post-contrast imaging series. At the discretion of the investigator, T1- and T2-weighted fast scanning sequences were also acquired. However, since the sponsor is not seeking approval of this agent for these image sequences and because of the potential biases associated with the manner in which these images were collected, this review will not address the evaluation of the T1- and T2-weighted fast scanning images. Instead emphasis will be placed on the evaluation of the T1-weighted spin-echo MR images since they are pertinent to the indication desired by the sponsor.

Baseline history and physical examinations were performed within 72 hours before the subjects ingested FerriSeltz. Blood and urine samples were collected for analysis within 24 hours before ingestion of FerriSeltz. Vital signs were monitored immediately before and 30-60 minutes after ingestion of FerriSeltz. Subjects returned 24 hours after FerriSeltz ingestion for measurement of vital signs, collection of blood and urine samples, and questioning about any adverse experiences following dosing. According to the sponsor, subjects with abnormal findings were followed until their measurements returned to baseline.

As part of the original study protocol, the subjects' images were to be evaluated by the site investigators as well as by a blinded reader (a different blinded reader was used for each study).

The site investigators (unblinded to dose) evaluated the pre- and post-dose images side-by-side and rated the degree of improvement in signal intensity, opacification, signal homogeneity, distention, and delineation of gastrointestinal tract in three regions, the stomach, duodenum, and jejunum. The degree of improvement in the

delineation of the gastrointestinal tract was also rated for the stomach wall, bowel wall, head of pancreas, tail of pancreas, and body of pancreas. Possible ratings for the improvement in these parameters were 'none', 'minimal', 'moderate', or 'significant'. Note that this rating scale does not allow for the possibility that the quality of these variables was worse on the post-dose images than on the pre-dose images. This may have introduced bias in the summary statistics (e.g. mean, proportion, etc.) in favor of the contrast enhanced images.

The blinded readers (blinded to clinical history, site, and dose level) rated the same parameters as the site investigators. However, unlike the site investigators, the blinded readers evaluated the images in an unpaired fashion using various scales[1]. The order in which the blinded readers evaluated the images was randomized with respect to pre- and post-dose images, dose level, and investigational site. The differences in the ratings from pre- to post-dose were analyzed. It should be noted that not all of the subjects who were enrolled and imaged in this trial were evaluated by the blinded readers. The sponsor wished to limit the duration of the blinded readers' review so the sponsor amended the original protocol to set a cutoff date for a subject's eligibility to be part of the blinded review. Thirty-eight subjects in Study A and eight subjects in Study B enrolled in the trial after the cutoff date and therefore were not evaluated by the blinded reviewers. In August of 1994, FDA statisticians suggested to the sponsor that the 46 images which were omitted from the blinded review should be blindly read and included in the analysis.

In response to an FDA request for information concerning the clinical utility of FerriSeltz, the sponsor re-evaluated images from these two trials. Pre- and post-dose scans were assessed independently by two blinded readers (not the same readers who participated as the blinded readers for the original protocol). The images were presented to the readers randomized with respect to pre- and post-dose images, dose level, and investigational site. The blinded reviewers assessed the stomach, duodenum, and pancreas in each image for the presence or absence of pathology using a five point scale (1 = definitely normal, 2 = probably normal, 3 = uncertain, 4 = probably abnormal, 5 = definitely abnormal). These image diagnoses were compared to "gold standard" diagnoses which were developed by a Clinical Trials Consultant using all available confirmatory diagnostic data contained in hospital records (including discharge summaries and copies of laboratory tests)

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[1] The rating scales used by the blinded readers to evaluate each efficacy parameter follow:
Signal Intensity: 0 = dark/air, 1 = soft tissue, 2 = intermediate, 3 = body fat, 4 = bright
Opacification: 0 = unmarked, 1 = faintly marked, 2 = moderately, 3 = clearly marked
Signal Homogeneity: 0 = N/A or low intensity, 1 = patchy/compromises interpretation, 2 = slightly patchy/acceptable, 3 = uniform in regions of high intensity
Distention: 1 = collapsed, 2 = partially filled, 3 = distended
Delineation: 0 = indistinct, 1 = minimal, 2 = moderate, 3 = clear distinction

and readings of diagnostic procedures (from CT, ultrasound, endoscopy, biopsy tests, and in some cases the pre-dose MRI image). Since in some cases, the pre-dose MR image was used to develop the "gold standard" diagnosis, the "gold standard" diagnosis may have agreed with the pre-dose image diagnosis more often than was appropriate. As long as the data from the aforementioned sources were not conflicting, the diagnosis was made by the consultant. When any of the above information was conflicting, a consensus diagnosis from three expert radiologists (other than the consultant) was used. The sponsor did not indicate how many subjects had conflicting information and were therefore diagnosed by the panel of experts.

III. Subject Enrollment and Resulting "Analysis Groups"

Two hundred seventy five subjects were enrolled in these trials (160 in Study A and 115 in Study B). As illustrated in Figures 1 and 2 below, 153 subjects in Study A and 114 subjects in Study B had images which were evaluated by the site investigators. The images from 115 subjects from Study A and 103 subjects from Study B were evaluated by the blinded readers. The most frequently reported reason for not including a subject in the blinded readers' evaluation was that the subject enrolled after the cutoff date listed in a protocol amendment to limit the duration of the blinded readers' evaluations.

Figure 1: Number of Subjects in Study A who were Included in the Site Investigators' Evaluation Group and in the Blinded Reader's Evaluation Group

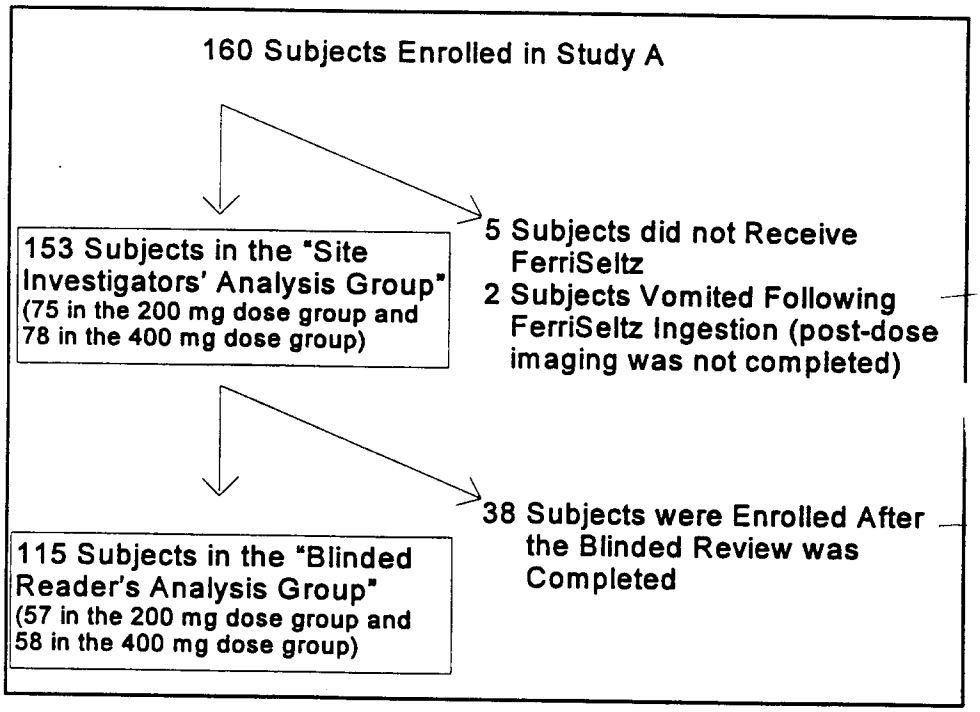
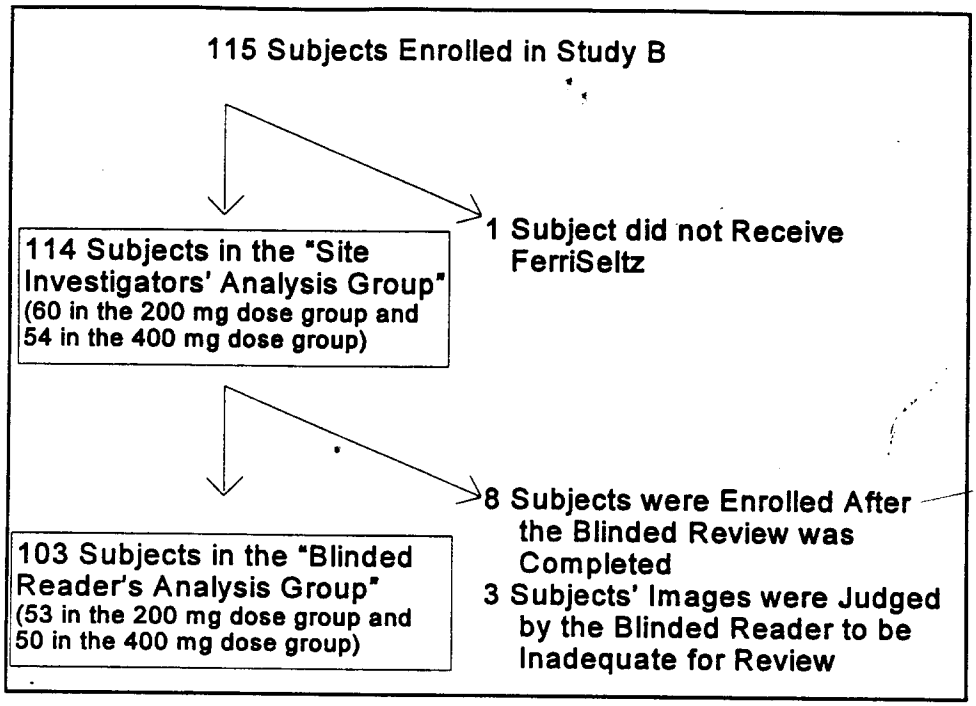


Figure 2: Number of Subjects in Study B who were Included in the Site Investigator's Evaluation Group and in the Blinded Reader's Evaluation Group



All subjects from both trials were included in the retrospective re-evaluation of the images as long as a "gold standard" diagnosis could be established. "Gold standard" diagnoses were established for 151 of the 160 subjects enrolled in Study A and for 113 of the 115 subjects enrolled in Study B. Although the subjects in Studies A and B were originally randomized to one of the two doses, the two dose groups were combined for this analysis. The sponsor justified this on the basis that bowel marking and organ delineation studies showed similar effectiveness of the agent in both dose groups.

IV. Efficacy Results

Site Investigators' Analysis

Because of the fact that the site investigators' evaluations of the images were unblinded paired evaluations and utilized a rating scale which only measure pre to post *improvement*, the data from the site investigators' evaluations of the images is most likely the least reliable of the three data sets submitted by the sponsor. Therefore, discussion of this data set will be included only as an appendix to this review.

Blinded Readers' Analysis

The blinded readers rated the signal intensity, opacification, signal homogeneity,

distention, and delineation of the pre- and post-dose image series. In addition, the blinded readers rated delineation in the stomach wall and bowel wall and in the head, tail, and body of the pancreas for the pre- and post-dose image series. In this review, the pre-dose image series is referred to as the pre-dose image. Similarly, the post-dose imaging slices are collectively referred to as the post-dose image. Note that the ratings assigned by the blinded readers are assessments of the qualities of an image series as a whole rather than ratings of an individual slice. Unlike the site investigators, the blinded readers evaluated the images in an unpaired fashion. The differences in the ratings from pre- to post-dose were analyzed. Thirty-eight subjects in Study A and eight subjects in Study B were not evaluated by the blinded readers because they enrolled in the trials after the cut-off date set to limit the duration of the blinded review.

The differences in the ratings from pre- to post-dose were analyzed using the Wilcoxon signed-rank test. Technically due to the number of comparisons being made, an adjustment for multiple comparisons is necessary. However, since these endpoints are highly correlated and the associated p-values are very low, this adjustment would make little difference in the overall result. **The post-dose image ratings were found to be statistically significantly better than the pre-dose images for signal intensity, opacification, signal homogeneity, and distention in all three anatomical sites, stomach, duodenum, and jejunum in both studies and both dose groups ($p \leq 0.001$ for all 48 comparisons).**

The delineation of the post-dose images was found to be statistically significantly better than the pre-dose images for some region-dose-study combinations. In Study A, all 16 region and dose group combinations showed statistically significant improvement in delineation ($p \leq 0.001$ for all 16 comparisons except for the 6 g FerriSeltz dose group and bowel wall region where $p = 0.008$). In Study B, in the 6 g FerriSeltz dose group, delineation was significantly improved for 5 of the 8 comparisons i.e., for the duodenum ($p < 0.001$), jejunum ($p = 0.005$), bowel wall ($p = 0.004$), head of the pancreas ($p = 0.018$), and tail of the pancreas ($p = 0.012$). For the 12 g FerriSeltz dose group in Study B, delineation was improved for 4 of the 8 comparisons i.e., the stomach ($p = 0.005$), stomach wall ($p < 0.001$), jejunum ($p < 0.001$), and bowel wall ($p = 0.001$).

The sponsor conducted an intent-to-treat (ITT) analysis by assigning images which were not evaluated by the blinded readers a score of zero for all efficacy parameters in all regions (38 images in Study A, 8 in Study B). However, since the same score was assigned to the pre-dose image and the post-dose image, the difference from pre- to post-dose was zero. Therefore the results of the sponsor's ITT analysis did not differ from the per-protocol (PP) analysis.

An more appropriate ITT analysis was completed by this reviewer for Study A.

(Due to the small number of missing evaluations for Study B, the results of an ITT analysis in this instance would be essentially unchanged from that of the PP analysis.) Missing image evaluations were accounted for by assigning scores to the pre- and post-dose images such that the efficacy variable rating decreased by one category for the post-dose image compared to the pre-dose image. A summary of the results of this analysis follows in Table 1.

Table 1: ITT Analysis of Blinded Reader's Image Evaluations[1] for Study A

Region	Efficacy Parameter	Dose Level	
		6g FerriSeltz	12g FerriSeltz
Stomach	Signal Intensity	$p<0.0001$	$p<0.0001$
	Opacification	$p<0.0001$	$p<0.0001$
	Signal Homogeneity	$p<0.0001$	$p<0.0001$
	Distention	$p<0.0001$	$p<0.0001$
	Delineation	$p<0.0001$	$p<0.0001$
Duodenum	Signal Intensity	$p<0.0001$	$p<0.0001$
	Opacification	$p<0.0001$	$p<0.0001$
	Signal Homogeneity	$p<0.0001$	$p<0.0001$
	Distention	$p=0.0009$	$p<0.0001$
	Delineation	$p=0.0003$	$p<0.0001$
Jejunum	Signal Intensity	$p<0.0001$	$p<0.0001$
	Opacification	$p<0.0001$	$p<0.0001$
	Signal Homogeneity	$p=0.0024$	$p=0.0005$
	Distention	$p=0.4600$	$p=0.2200$
	Delineation	$p=0.1400$	$p=0.0370$
Bowel Wall	Delineation	$p=0.5500$	$p=0.1700$
Stomach Wall	Delineation	$p<0.0001$	$p<0.0001$
Pancreas Head	Delineation	$p=0.0062$	$p=0.0001$
Pancreas Body	Delineation	$p=0.0017$	$p=0.0580$
Pancreas Tail	Delineation	$p=0.0660$	$p=0.2100$

1. ITT analysis was completed by this reviewer by assigning the images with missing evaluations scores which decreased by 1 category from pre- to post-dose.

Comparisons between dose groups were made using the Wilcoxon rank-sum test. Overall, 20 comparisons were made as part of this analysis therefore, standards require that a multiple comparison adjustment in the significance level of the tests be made. However, since these endpoints are highly correlated and the associated

p-values are very small, accounting for multiple comparisons would make little difference in the overall result. **The higher dose is significantly better than the lower dose for signal intensity, opacification, and signal homogeneity of the duodenum in Study A ($p=0.002$, $p<0.001$, and $p=0.004$ respectively). None of the dose comparisons in Study B were statistically significant even without an adjustment for multiple comparisons.**

The blinded readers also rated the image quality (inadequate, poor, good, excellent) and artifacts (severe, moderate, minimal, none). Tables 2 and 3 below contain these ratings and the p-values comparing the pre- and post-dose images.

Table 2: Pre- and Post-Dose Image Quality by Dose Level [1]

	Study A				Study B			
	6 g FerriSeltz		12 g FerriSeltz		6 g FerriSeltz		12 g FerriSeltz	
	Pre N=57	Post N=57	Pre N=58	Post N=58	Pre N=53	Post N=53	Pre N=50	Post N=50
Quality of Images for iologic Interpretation								
4 = Excellent	30	26	31	26	12	8	17	6
3 = Good	21	24	23	27	28	23	24	35
2 = Poor	6	7	4	5	13	21	8	8
1 = Inadequate	0	0	0	0	0	1	0	0
Missing [2]	0	0	0	0	0	0	1	1
p-value [3]	0.329		0.208		0.013		0.034	

1. This table was created based on data in the sponsor's submission.
2. The quality of this image was not evaluated by the blinded reader. A reason for this omission was not provided in the sponsor's submission.
3. Changes from pre- to post-dose were evaluated using Wilcoxon signed-rank test.

No significant differences were found between doses in the quality of the images for radiologic interpretation. However, as indicated in Table 2, a statistically significant decrease from pre- to post-dose in the quality of the images was found in Study B ($p=0.013$ for the low dose group, $p=0.034$ for the high dose group). These relationships were verified by this reviewer using an exact test. Though not statistically significant in Study A the pre to post difference trended in the same direction. **These results imply that the blinded readers felt the quality of the pre-dose image for radiologic interpretation was better than that of the post-dose image.**

Table 3: Artifact/Effect on Interpretation of Pre- and Post-Images by Dose Level [1]

	Study A				Study B			
	6 g FerriSeltz		12 g FerriSeltz		6 g FerriSeltz		12 g FerriSeltz	
	Pre N=57	Post N=57	Pre N=58	Post N=58	Pre N=53	Post N=53	Pre N=50	Post N=50
Artifact/Effect on Interpretation								
1 = None or no effect	38	24	41	28	12	11	15	7
2 = Minimal	13	20	10	20	27	18	28	26
3 = Moderate	6	9	5	9	10	12	6	14
4 = Severe	0	3	1	1	4	10	0	3
Missing [2]	0	1	1	0	0	2	1	0
p-value [3]	0.001		0.021		0.029		<0.001	

1. This table was created based on data in the sponsor's submission.
2. The extent of artifact/effect on interpretation was not evaluated by the blinded reader for these images. Reasons for these omissions were not provided in the sponsor's submission.
3. Changes from pre- to post-dose were evaluated using Wilcoxon signed-rank test.

No significant differences were found between doses in the artifact/effect on interpretation. However, as indicated in Table 3, a statistically significant increase from pre- to post-dose in the artifact/effect on interpretation was found in both Study A ($p=0.001$ for the low dose group, $p=0.021$ for the high dose group) and Study B ($p=0.029$ for the low dose group, $p<0.001$ for the high dose group). These relationships were verified by this reviewer using an exact test. **These results indicate that the blinded readers felt the artifact/effect on interpretation seen for the pre-dose image was less than that of the post-dose image.**

Pre- and Post-Dose Image Diagnoses Compared to "Gold Standard Diagnoses"

The clinical utility of FerriSeltz was assessed based on a re-evaluation of the image sets from these two trials. The 6 g and 12 g FerriSeltz dose groups were combined for this analysis. The pre- and post-dose image sets were assessed randomly (randomized with respect to pre- and post-dose, dose level, and investigational site) and independently by two blinded readers who rated the stomach, duodenum, and pancreas for each image set using a five point scale (1 = definitely normal, 2 = probably normal, 3 = uncertain, 4 = probably abnormal, 5 = definitely abnormal). The five point scale listed above was reduced to a three point scale as per protocol, by defining a score of 1 or 2 on the previous scale as "normal", 4 or 5 was listed as "abnormal", and 3 remained "uncertain". These image diagnoses were compared to "gold standard" diagnoses which were developed by a Clinical Trials Consultant using all available confirmatory diagnostic data. In some cases the pre-

dose MRI image was used to develop the "gold standard" diagnosis. This could cause the "gold standard" diagnosis to agree with the pre-dose image diagnosis more often than is appropriate. When any of the confirmatory diagnostic data was conflicting, the consensus of three expert radiologists (the "Clinical Trials Consultant" was not included) was used as the "gold standard" diagnosis. The sponsor did not provide the number of cases which involved conflicting information and were referred to the expert panel for diagnosis.

Tables 3, 4, and 5 contain the comparison of the pre- and post-dose image diagnoses to the gold standard diagnoses for each anatomical region (stomach, duodenum, and pancreas, respectively) by each blinded reader. The data for Studies A and B have been combined for this analysis.

Calculating sensitivity and specificity estimates from this data is not appropriate due to the large number of "uncertain" diagnoses. Therefore, the comments following Tables 3, 4, and 5 address the relationships between actual cell frequencies rather than sensitivity and specificity measurements. Specifically it is noted how many "uncertain" pre-image diagnoses fell into correct diagnoses using the post-image and if this proportion is statistically significant.

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Table 3: Comparison of Pre- and Post-Dose Image Diagnoses to the "Gold Standard Diagnoses" for the Stomach Region [1]

Blinded Reader #1			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	84	1
		Uncertain	159	11
		Abnormal	2	4

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	220	5
		Uncertain	16	5
		Abnormal	9	6

Blinded Reader #2			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	20	0
		Uncertain	220	15
		Abnormal	5	1

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	188	3
		Uncertain	47	4
		Abnormal	10	9

1. Table was created by the statistical reviewer.

The following conclusions **regarding the stomach region** were noted using the data in Table 3:

(1.) There were 159 (BR#1) and 220 (BR#2) uncertain pre-image diagnoses which according to the gold standard were truly normal. Of the post-dose images, 140/159 = 88.05% CI: (81.97%, 92.65%) (BR#1) and 170/220 = 77.27% CI: (71.16%, 82.64%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, is statistically significant in the stomach region for subjects with normal gold standard diagnoses ($p < 0.0001$ for BR#1 and BR#2). Conclusion: The use of FerriSeltz aids in the recognition of normal images where without the drug the images may have been inconclusive.

(2.) The number of images for which the gold standard was abnormal and the pre-image diagnosis was uncertain was, 11 (BR#1) and 15 (BR#2). Of the post-dose images, 4/11 = 36.36% CI: (10.93%, 69.21%) (BR#1) and 8/15 = 53.33% CI: (26.59%, 78.73%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, for subjects with abnormal gold standard diagnoses is not statistically significant for BR#1 ($p = 0.097$) but is significant for BR#2 ($p = 0.004$). Conclusion: Although the number of subjects with abnormal gold standard diagnoses is small, it appears (at least according to BR#2) that FerriSeltz is advantageous in the identification of abnormal images where without the drug the images may have been inconclusive.

Table 4: Comparison of Pre- and Post-Dose Image Diagnoses to the "Gold Standard Diagnoses" for the Duodenum Region [1]

Blinded Reader #1			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	165	2
		Uncertain	91	2
		Abnormal	0	1

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	223	4
		Uncertain	32	0
		Abnormal	1	1

Blinded Reader #2			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	66	1
		Uncertain	187	3
		Abnormal	3	1

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	144	2
		Uncertain	100	0
		Abnormal	12	3

1. Table was created by the statistical reviewer. Some results are partially based on imputed data.

The following conclusions **regarding the duodenum region** were noted using the data in Table 3:

(1.) There were 91 (BR#1) and 187 (BR#2) uncertain pre-image diagnoses which according to the gold standard were truly normal. Of the post-dose images, 68/91 = 74.73% CI: (64.53%, 83.25%) (BR#1) and 108/187 = 57.75% CI: (50.33%, 64.93%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, is statistically significant in the duodenum region for subjects with normal gold standard diagnoses ($p < 0.0001$ for BR#1 and $p = 0.0403$ BR#2). Conclusion: The use of FerriSeltz aids in the recognition of normal images where without the drug the images may have been inconclusive.

(2.) The number of images for which the gold standard was abnormal and the pre-image diagnosis was uncertain was 2 (BR#1) and 3 (BR#2). Of the post-dose images, 0/2 = 0.00% CI: (0.00%, 84.19%) (BR#1) and 2/3 = 66.67% CI: (9.43%, 99.16%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. These results were was not statistically significant ($p = 0.50$ for BR#1 and $p = 1.0$ for BR#2). Conclusion: Since the number of subjects with abnormal gold standard diagnoses is small, the data is not sufficient to demonstrate whether FerriSeltz is advantageous in the identification of abnormal images for those subjects who had uncertain pre-dose image diagnoses.

Table 5: Comparison of Pre- and Post-Dose Image Diagnoses to the "Gold Standard Diagnoses" for the Pancreatic Region [1]

Blinded Reader #1		Gold Standard Diagnosis	
Pre-Dose Image Diagnosis		Normal	Abnormal
	Normal	153	12
	Uncertain	60	10
	Abnormal	6	22

		Gold Standard Diagnosis	
Post-Dose Image Diagnosis		Normal	Abnormal
	Normal	179	14
	Uncertain	27	7
	Abnormal	13	23

Blinded Reader #2		Gold Standard Diagnosis	
Pre-Dose Image Diagnosis		Normal	Abnormal
	Normal	148	9
	Uncertain	60	14
	Abnormal	11	21

		Gold Standard Diagnosis	
Post-Dose Image Diagnosis		Normal	Abnormal
	Normal	157	10
	Uncertain	47	11
	Abnormal	15	23

1. Table was created by the statistical reviewer. Some results partially based on imputed data.

The following conclusions **regarding the pancreatic region** were noted using the data in Table 3:

(1.) There were 60 (BR#1) and 60 (BR#2) uncertain pre-image diagnoses which according to the gold standard were truly normal. Of the post-dose images, 39/60 = 65.00% CI: (51.60%, 76.87%) (BR#1) and 38/60 = 63.33% CI: (49.90%, 75.41%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, is statistically significant in the pancreatic region for subjects with normal gold standard diagnoses for BR#1 ($p = 0.0273$) but not for BR#2 ($p = 0.0519$). Conclusion: The use of FerriSeltz (at least according to BR#1) aids in the recognition of normal images where without the drug the images may have been inconclusive.

(2.) The number of images for which the gold standard was abnormal and the pre-image diagnosis was uncertain was, 10 (BR#1) and 14 (BR#2). Of the post-dose images, 3/10 = 30.00% CI: (6.67%, 65.25%) (BR#1) and 6/14 = 42.86% CI: (17.66%, 71.14%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. These results were not statistically significant ($p = 0.3438$ for BR#1, $p = 0.7905$ for BR#2). Conclusion: Since the number of subjects with abnormal gold standard diagnoses is small, the data is not sufficient to demonstrate whether FerriSeltz is advantageous in the identification of abnormal images for those subjects who had uncertain pre-dose image diagnoses.

V. Safety Results

The number of adverse events experienced in each dose group and study are presented in Table 6. Thirty-five percent (54/155) of patients in Study A reported a total of 85 adverse events. In Study B, 25% (29.114) of patients reported a total of 43 adverse events. In both studies, the highest proportion of adverse events was reported for the digestive system (32% in Study A, 21% in Study B). In Study A, there was a statistically significantly higher proportion of digestive system adverse events in the 12 g FerriSeltz dose group when compared to that of the 6 g FerriSeltz dose group.

Table 6: Incidence of Adverse Events by Body System and Study [1]

Body System / Adverse Event	Study A Total Adverse Events 6 g FerriSeltz	Study A Total Adverse Events 12 g FerriSeltz	Study B Total Adverse Events 6 g FerriSeltz	Study B Total Adverse Events 12 g FerriSeltz
Number of Patients Assessed	76	79	60	54
Number of Patients Experiencing Adverse Events	21 (28%)	33 (42%)	13 (22%)	16(30%)
Body as a Whole	4 (5%)	8 (10%)	4 (7%)	1 (2%)
fever	0 (0%)	1 (1%)	0 (0%)	0 (0%)
headache	3 (4%)	4 (5%)	2 (3%)	1 (2%)
pain	1 (1%)	3 (4%)	2 (3%)	0 (0%)
diovascular	2 (3%)	1 (1%)	0 (0%)	1 (2%)
hypotension	1 (1%)	0 (0%)	0 (0%)	0 (0%)
sickle crisis	0 (0%)	0 (0%)	0 (0%)	1 (2%)
tachycardia	2 (3%)	1 (1%)	0 (0%)	0 (0%)
Digestive	17 (22%) [2]	32 (41%) [2]	10 (17%)	14 (26%)
constipation	1 (1%)	0 (0%)	2 (3%)	0 (0%)
diarrhea	9 (12%)	23 (29%)	5 (8%)	13 (24%)
dyspepsia	1 (1%)	0 (0%)	0 (0%)	0 (0%)
flatulence	1 (1%)	1 (1%)	0 (0%)	0 (0%)
nausea	5 (7%)	6 (8%)	1 (2%)	3 (6%)
pain, abdominal	3 (4%)	8 (10%)	1 (2%)	2 (4%)
pain, rectal	0 (0%)	0 (0%)	0 (0%)	1 (2%)
vomiting	1 (1%)	3 (4%)	2 (3%)	0 (0%)
Nervous System	1 (1%)	0 (0%)	2 (3%)	0 (0%)
anxiety	0 (0%)	0 (0%)	1 (2%)	0 (0%)
convulsions	0 (0%)	0 (0%)	1 (2%)	0 (0%)
insomnia	1 (1%)	0 (0%)	1 (2%)	0 (0%)
Respiratory System	0 (0%)	2 (3%)	1 (2%)	0 (0%)
coughing	0 (0%)	1 (1%)	0 (0%)	0 (0%)
epistaxis	0 (0%)	0 (0%)	1 (2%)	0 (0%)
rhinitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)
enital System	1 (1%)	0 (0%)	0 (0%)	1 (2%)
dysmenorrhea	1 (1%)	0 (0%)	0 (0%)	0 (0%)
infection (UTI)	0 (0%)	0 (0%)	0 (0%)	1 (2%)

1. This table with minor modifications in format was submitted by the sponsor.
2. The incidence of digestive system adverse events was statistically significantly higher in the 12 g FerriSeltz group th[illegible] the 6 g FerriSeltz group (p=0.017)

VI. Conclusions

From a statistical perspective, conclusions regarding the primary and secondary endpoints favor the use of FerriSeltz as an adjunctive imaging agent. However, other comparisons indicated that the post-contrast agent images were inferior to the pre-contrast images with regard to image quality and artifacts.

The following conclusions are based on the blinded readers' evaluations of the pre- and post-dose images.

- The post-dose images are statistically significantly better than the pre-dose images for *signal intensity, opacification, signal homogeneity, and distention in all three anatomical sites, stomach, duodenum, and jejunum* in both studies and both dose groups ($p \leq 0.001$ for all 48 comparisons). The *delineation* of the post-dose images are statistically significantly better than the pre-dose images for 25 of the 32 region-dose-study combinations (the p-value varies across the region, dose, and study combinations).

- The results of Study A indicate that the *higher dose of FerriSeltz is statistically significantly better than the lower dose for signal intensity and opacification of the duodenum* ($p = 0.002$ and $p < 0.001$, respectively). This relationship is not confirmed by the results of Study B.

- The results of Study B reveal a *statistically significant decrease from pre- to post-dose in the quality of the images* ($p = 0.013$ for the low dose group, $p = 0.034$ for the high dose group). Such a relationship is not confirmed by Study A. These results seem to imply that the quality of the pre-dose images for radiologic interpretation is better than that of the post-dose images.

- The results of both Study A and B reveal a *statistically significant increase from pre- to post-dose in the artifact/effect on interpretation* ($p = 0.001$ for the low dose group in Study A, $p = 0.021$ for the high dose group in Study A, $p = 0.029$ for the low dose group in Study B, $p < 0.001$ for the high dose group in Study B). These results indicate that the artifact/effect on interpretation seen for the pre-dose image is less than that of the post-dose image.

The following conclusions are based on the comparisons of the pre- and post-dose image diagnoses to the gold standard diagnoses:

- FerriSeltz seems to be advantageous in correctly determining that a subject is *normal* where without FerriSeltz, that patients' images may have been

- FerriSeltz seems to be advantageous in correctly determining that a subject is *normal* where without FerriSeltz, that patients' images may have been inconclusive. This relationship is statistically significant for both blinded readers in all three regions studied ($p<0.001$ in all cases) except for blinded reader 2's assessment of the pancreatic region ($p=0.269$).

- Because of the small number of subjects with true abnormalities (as judged by the gold standard), it is not possible to conclude from this data whether FerriSeltz is advantageous in correctly determining that a subject is *abnormal* when without FerriSeltz, that patients' images may have been inconclusive. This type of relationship is statistically significant in these studies in only one instance; the stomach region as assessed by blinded reader 2 ($p=0.004$). However, it is possible that in a study with a larger number of truly abnormal subjects, this relationship could become statistically significant in the other regions as well.

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cc:
Archival NDA#20-292
HFD-160/P. Love
HFD-160/V. Raczkowski
HFD-160/E. Jones
HFD-160/S. Chow
HFD-160/S. Cusack
HFD-160/File Copy
HFD-344/A. Lisook
HFD-720/Chron. Copy
HFD-720/N. Smith
HFD-720/M. Welch
HFD-720/R. Davi
HFD-720/File Copy
R. Davi/827-3122/WordPerfect/08/19/96
This review contains 21 pages of text, tables, and figures.

Appendix A

Discussion of the Site Investigators' Evaluation of the Images

Site Investigators' Image Evaluation

The unblinded site investigators evaluated the pre- and post-dose images side-by-side and rated the degree of improvement in signal intensity, opacification, signal homogeneity, distention, and delineation of gastrointestinal tract in three regions, the stomach, duodenum, and jejunum. Delineation was also rated for the stomach wall and bowel wall. The site investigators had the following categories as options to assign to each pair of images to describe the 'improvement' from pre- to post-dose: none, minimal, moderate, and significant. Figures 1 through 5 below illustrate the ratings assigned by the site investigators for Study A. Figures 6 through 10 illustrate these scores for Study B. Note that because the rating scale for this analysis did not allow the investigators the option to rate the post-dose images as being worse than the pre-dose images, the data portrayed in Figures 1 through 10 may be artificially inflated.

Because of the fact that the site investigators' evaluations of the images were unblinded paired evaluations and utilized a rating scale which was not properly designed, the data set portrayed in Figures 1 through 10 is most likely the least reliable of the data sets (site investigators' image evaluations, blinded readers' image evaluations, and the gold standard comparisons) submitted by the sponsor. However, it may still be worth noting the following trends which seem to be appearing in this data.

(1.) When comparing the dose groups for each parameter across each anatomical region (a total of 17 comparisons in each study) using the Wilcoxon rank-sum test, the scores for the 12 g FerriSeltz group are statistically significantly better than for the 6 g FerriSeltz group for the following parameters and anatomical regions:

For Study A:

Signal Intensity ($p = 0.019$), Opacification ($p = 0.015$), Homogeneity ($p = 0.033$), and Delineation ($p = 0.013$) in the stomach region.

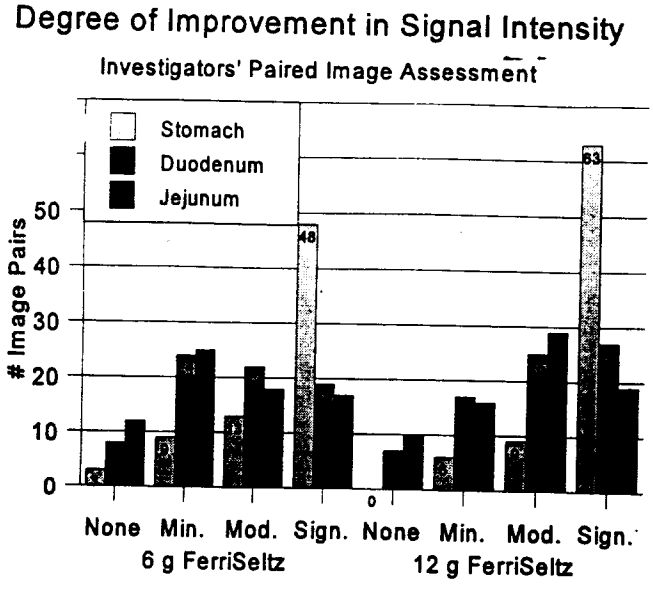
For Study B:

Signal Intensity ($p = 0.044$), Opacification ($p = 0.019$), Homogeneity ($p = 0.038$), and Delineation ($p = 0.043$) in the jejunum region as well as Homogeneity ($p = 0.033$) in the duodenum region.

It is not unusual however, that four or five statistically significant results would be found when this number of multiple comparisons are being made, even if there is no true difference in the dose groups. In fact, if the significance levels of the tests were adjusted to account for multiple comparisons, the p-values which are greater than 0.003 would no longer be considered statistically significant.

(2.) From visual observation of the graphs in Figures 1 through 10, it appears that FerriSeltz is adding some degree of improvement for most parameters in the stomach region and for delineation of the stomach wall as illustrated by the 'moderate' and 'significant' columns in the histograms being taller than the 'mild' or 'none' columns for both dose groups for these regions. It is not visually apparent that there is improvement being added in other regions (duodenum and jejunum) as the 'moderate' and 'significant' columns in the histograms are not markedly taller than the 'mild' or 'none' columns for these regions.

Figure 2 (Study A)



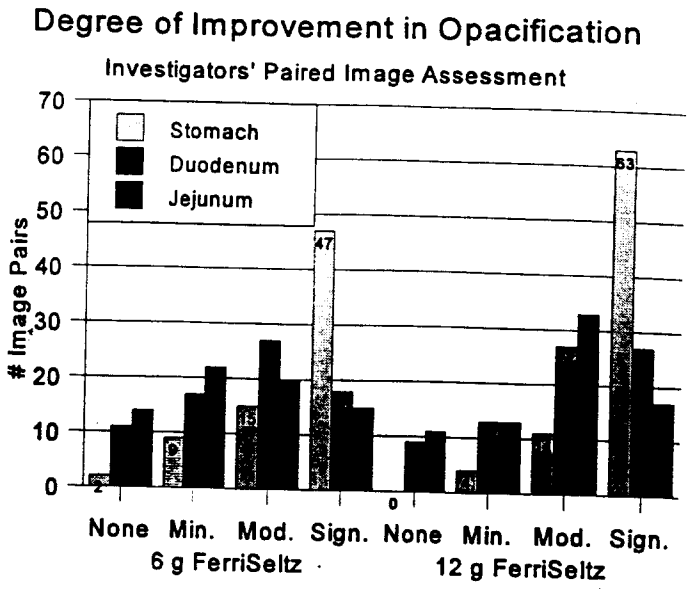
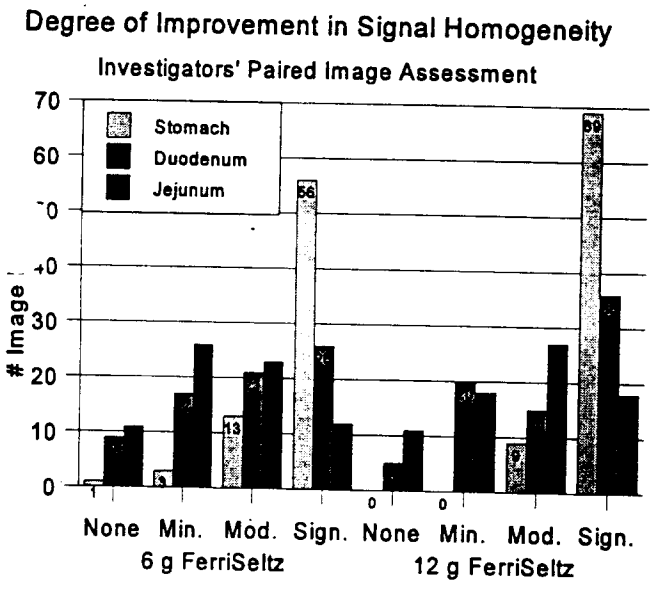


Figure 3 (Study A)

Figure 4 (Study A)



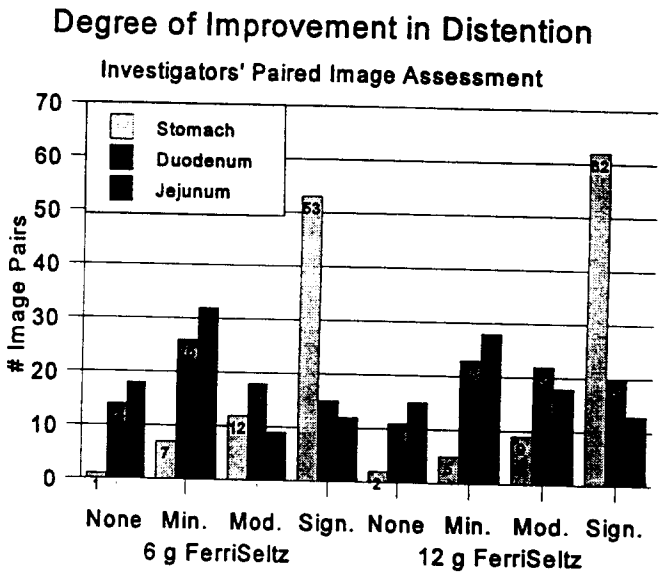


Figure 5 (Study A)

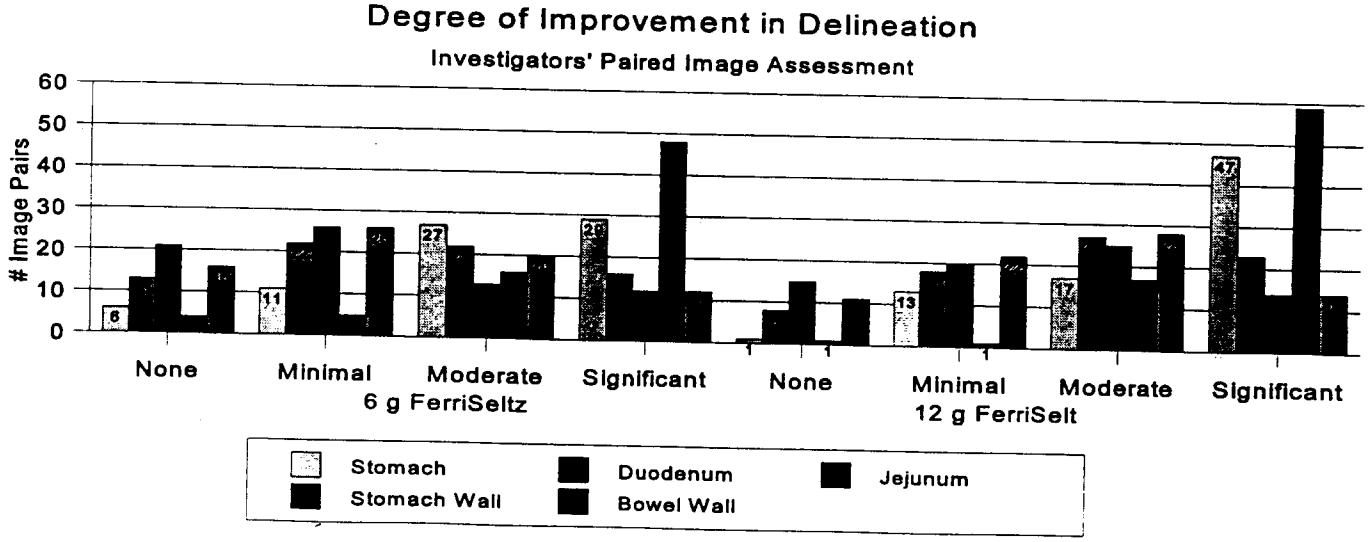
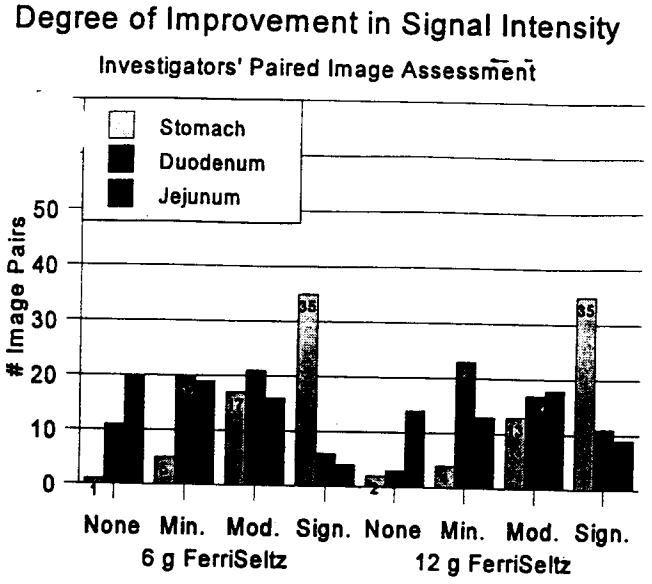


Figure 7 (Study B)



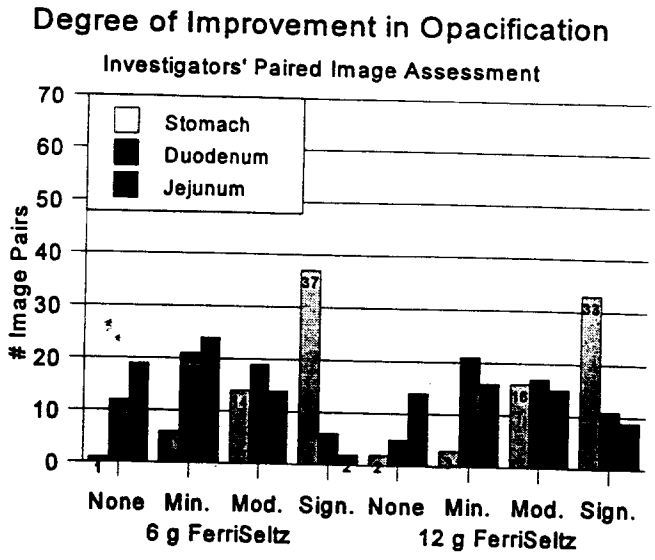
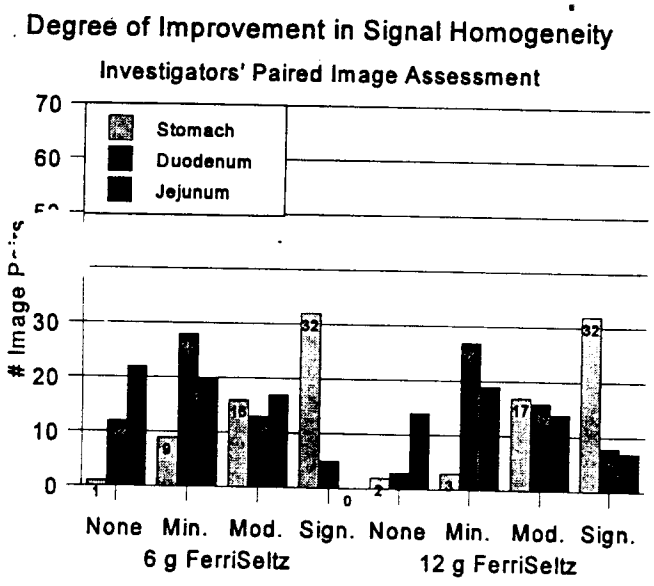


Figure 8 (Study B)

Figure 9 (Study B)



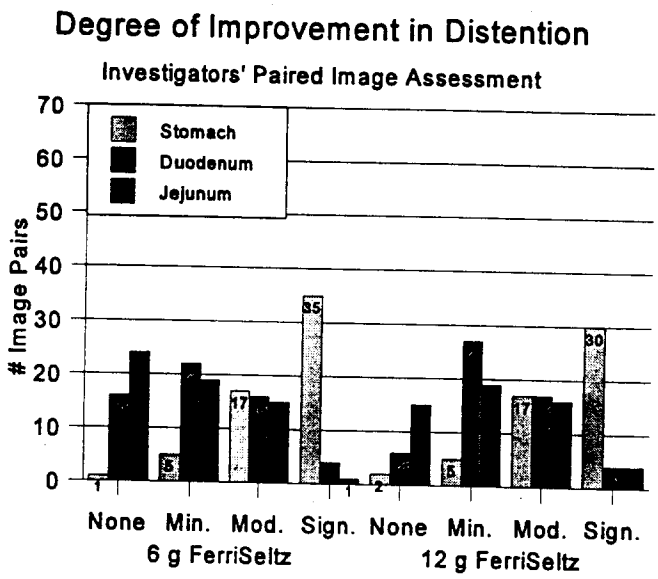
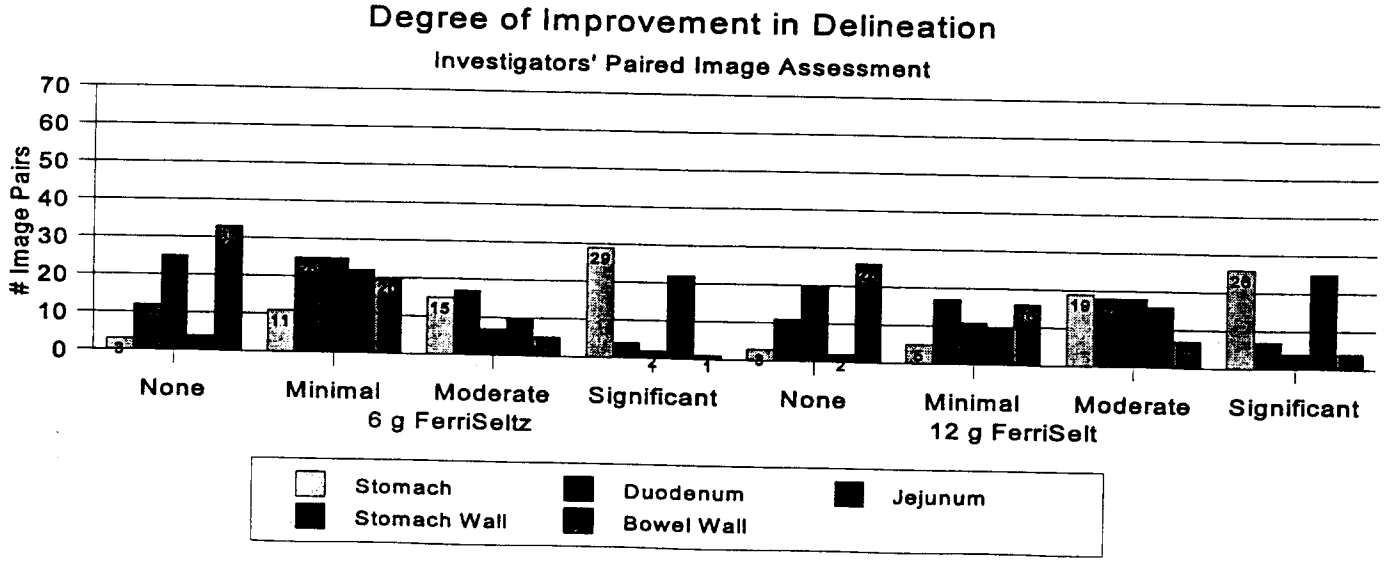


Figure 10 (Study B)



The delineation of the head, tail, and body of the pancreas was also scored by the site investigators. The scores for the 'improvement' in delineation of the pancreas for the pre- and post-dose image pairs follow in Figures 11 and 12. Hypothesis tests comparing dose groups and testing the degree of 'improvement' in pre- and post-dose image pairs yielded no statistically significant results for either Study A or B in the pancreatic region.

Figure 11 (Study A)

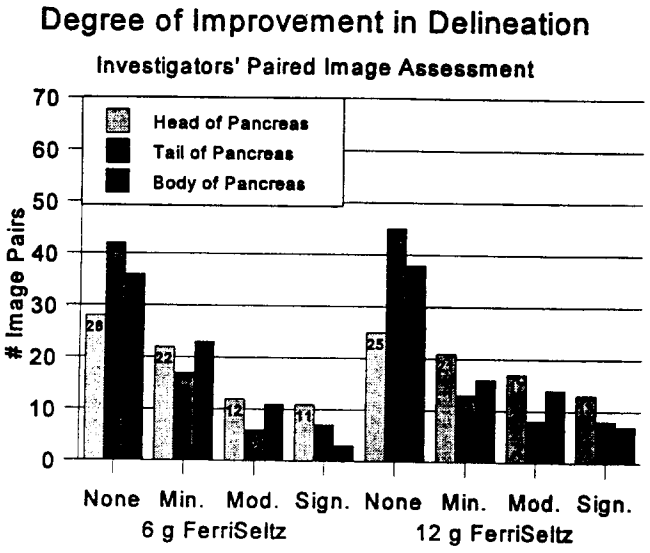
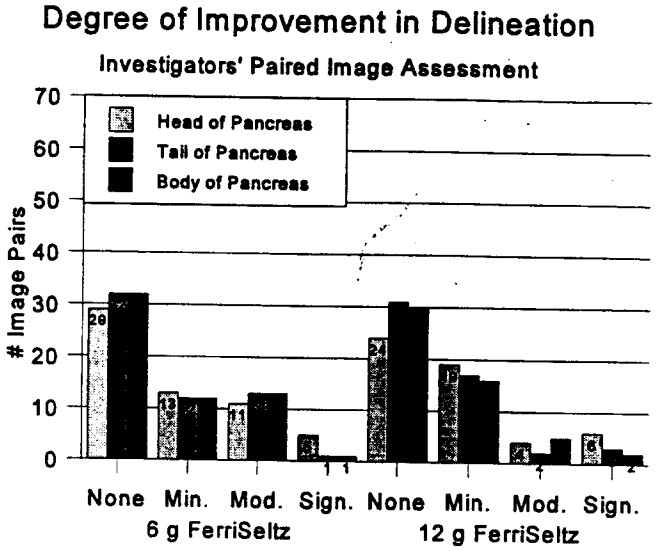


Figure 12 (Study B)



APPEARS THIS WAY
ON ORIGINAL

NOV 2 2 1993

NDA Statistical Consult

NDA#: 20,292

Applicant: Oncomembrane, Inc.

Name of Drug: Ferriseltz

Documents Reviewed: Sponsor's submission dated October 1, 1993

Indication: MR Imaging

Medical Input: HFD-160

The sponsor submitted an NDA for the above indication which was 'refused to file' on January 8, 1993. The sponsor submitted a plan for resubmission on June 4, 1993 inviting comments from the FDA. The present submission is a revised plan taking into account the comments and suggestions from HFD-160 and me.

The primary efficacy comparisons, as described on page 7 of the sponsor's submission, seem to me to be statistically sound. The first test, based on the number of correct diagnoses with the pre-and post- scans, tests for diagnostic capability and the second test, based on a comparison of pre- and post- scans, tests for contrast enhancement. I suggest that the Stuart-Maxwell test for ordered categories given by (8.20), page 123 of the reference at the end be used for contrast enhancement.

The secondary efficacy comparisons are based on the pre- and post-ROC curves as described on page 8 and in the appendix of their submission. The sponsor seems to suggest the following: Let = probability that the bootstrap simulated D exceeds the observed D where D= area under the post-ROC curve- area under the pre-ROC curve summed over the readers. An estimate of D is the ratio of the number of bootstrap simulated D's exceeding the observed D to the number of bootstrap simulations. If $\alpha < .05$, we conclude that the post-scans are better than the pre-scans; otherwise, we conclude that the post-scans are no better than the pre-scans. If the simulations are done thousands of times, the procedure seems sound to me; but the conclusion should only be used as a confirmation of the Stuart-Maxwell test. The main reason is that this test is a conditional test and nothing is known about its power. Consequently, we do not know how good the test is.

The sponsor accepts suggestions (1) to (5) and questions suggestions (6) and (7) of my memorandum of consultation dated July 15, 1993. With respect to (6), I am prepared to go along with the sponsor's suggestion if my clarification in the second paragraph is right. As regards (7), if the diagnoses can be given only in terms of probabilities, there is no choice except

to rely on ROC curves. In such a case, definite values for sensitivity and specificity cannot be arrived at to examine whether they are close to 1 as I suggested. For ready reference, I am enclosing a copy of my memorandum dated July 15, 1993.

REFERENCE

Joseph L. Fleiss(1981). Statistical Methods for Ratios and Proportions, Second Edition. John Wiley and Sons.

R. Murty Ponnapalli, Ph.D.
Biomedical Statistician
Group 7

Concur: Nancy Smith, Ph.D.
11/22/93

cc:

Orig. NDA: 20,292
HFD-160
HFD-160/Dr. Blay
HFD-160/Dr. Love
HFD-160/Dr. Chow
HFD-713/Dr. Dubey [File DRU 1.3.1]
HFD-713/Dr. Smith
HFD-713/Dr. Ponnapalli
Chron.

This review contains 2 pages and an attachment.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF CONSULTATION

DATE: July 15, 1993

FROM: Biomedical Statistician (HFD-713)

THROUGH: Dr. Satya D. Dubey, Ph.D.
Chief, Statistical Evaluation and Research Branch
Division of Biometrics, CDER (HFD-713)

SUBJECT: Proposed plan for resubmission of NDA# 20-292

TO: File (NDA 20-292, Ferriselz)

The Division of Medical Imaging, Surgical and Dental Drug Products (HFD-160) refused to file the above NDA on January 8, 1993. In their letter dated June 4, 1993, the sponsors outlined a plan for resubmission of the NDA after reevaluation of the films taken before and after the administration of the contrast agent. Through this memorandum, I offer the following comments on the statistical aspects of the proposed protocol:

(1) For the primary objective of contrast assessment or image enhancement, one should <u>not</u> exclude patients for whom a gold standard assessment cannot be made.

(2) As suggested to me by the medical officer, I am in favor of <u>two</u> blinded radiologists reading the films instead of <u>three</u>. Not only does the assignment of batches to radiologists in a random fashion become simpler, but this also has implications on what the sponsors call summary level of significance as my subsequent comments will indicate.

(3) The primary efficacy comparisons on page 6 of their letter should also cover the films for pancreas.

(4) If, for both the studies, both reviewers' findings show evidence of positive effect of the contrast agent, each at level of significance .05, this will be sufficient evidence to claim enhancement of the film.

(5) I cannot see any use of the summary significance level obtained by the bootstrap method. The problem here is the following converse: In order that the summary significance level be .05, what significance levels should be chosen for each of the two radiologists? I do not think that the FDA will accept any solution to this problem obtained by the bootstrap method since it is at best only an estimate. Instead, I suggest that .05 be chosen as the level significance for each of the radiologists. It can then be easily seen that the summary level of significance is controlled at .05.

(6) The above comments of mine about bootstrap methodology also apply to the comparison of areas under ROC curves determined by the pre and post scans.

(7) To justify diagnostic claims for the agent, it appears to me that it is not enough if the proportion of "correct" diagnoses after the administration of the agent is statistically significantly better than before the administration. In my opinion, the sensitivity and the specificity after the administration of the agent should both be high (say >.8) to substantiate the diagnostic claim.

R. Murty Ponnapalli

R. Murty Ponnapalli, Ph.D.
Biomedical Statistician
Group 7

cc:
Orig. NDA 20-292
HFD-160
HFD-160/Dr. Chow
HFD-160/Ms. Kummerer
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr.Harkins
HFD-713/Dr. Ponnapalli
Chron.

This memorandum contains 2 pages.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

MICROBIOLOGY REVIEW(S)

APR 1 1996

REVIEW for DIVISION of MEDICAL IMAGING and RADIOPHARMACEUTICAL DRUG PRODUCTS
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805
MICROBIOLOGIST'S REVIEW NO. 1
April 1, 1996

MICROBIOLOGY REVIEWER: Carol K. Vincent

A. 1. NDA No.: 20-292

DRUG PRODUCT NAME: FerriSeltz (ferric ammonium citrate, brown)

APPLICANT: Oncomembrane, Inc.
201 3rd Avenue, Suite 3010
Seattle, WA 98101

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Dry powder to mix with water at point of use for oral ingestion.

3. METHOD(s) OF STERILIZATION:

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen.

5. DRUG PRIORITY CLASSIFICATION: 1 S

B. 1. DOCUMENT DATE: 11-15-95
2. AMENDMENT: 12-22-95
5. ASSIGNED: 03-08-96
4. RECEIVED FOR REVIEW: 03-11-96

C. REMARKS: The FDA asked the applicant to provide microbiological 'limits' information concerning the drug product. The December 22, 1995 amendment contains methods for and results from microbial limits testing on five lots of ferric ammonium citrate, brown [FAC] used in manufacturing the FerriSeltz drug product.

D. CONCLUSION: We recommend approval on the basis of microbiological quality. The information provided for microbial limits in the December 22, 1995 amendment is adequate; no further microbiological information is necessary for this product.

cc:
Orig. NDA 20-292
HFD-160/Consult/Chow/Salazar/Weir/Cusack
HFD-160/CKVincent [HFD-805]
Drafted by: CKVincent/03-11-96/30-29-96
R/D Init by: PHCooney/04-1-96
Filename: NDA20292

Carol K. Vincent 4/1/96
Carol K. Vincent
Review Microbiologist [HFD-805]

4/1/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-292 SUBMISSION DATE: 11/15/95

FERRIC AMMONIUM CITRATE, BROWN
FERRISELTZ®
2 OR 4 PACKETS (200 OR 400 MG ELEMENTAL IRON)

ONCOMEMBRANE, INC.
1201 THIRD AVE, SUITE 3010
SEATTLE, WASHINGTON 98101 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RE-SUBMITTED ORIGINAL NDA CODE: 3S

CONTENT PAGE

I. SYNOPSIS/BACKGROUND

NDA 20-292 for ferric ammonium citrate, brown (FerriSeltz®) was submitted by the sponsor on November 15, 1995. FerriSeltz®, a brownish-yellow powder is an oral iron formulation which is proposed as a contrast agent for marking the upper gastrointestinal tract in adult patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen. The sponsor proposes that following oral administration, ferric ammonium citrate, brown mixes with bowel contents and lowers the spin lattice (T_1) relaxation times thereby increasing intraluminal signal intensity on T^1-weighted magnetic resonance images. The package insert recommended doses of FerriSeltz® (2 or 4 packets) are 200 or 400 mg of elemental iron. It is also stated in the package insert that FerriSeltz® is to be administered following reconstitution with 600 mL of tap water and that patients should fast for at least 6 hours before receiving the drug.

For the treatment of iron deficiency anemia, the average daily oral dose of iron is about 200 mg (65 mg t.i.d.). The lethal dose of iron for humans is, on the average, 200-250 mg/kg. However, iron doses as low as 40 mg/kg have been known to be lethal in children. The maximum package insert iron dose (400 mg) in FerriSeltz® is equivalent to 8 mg Fe^{2+}/kg in a 50 kg person. In the CFR, ferric ammonium citrate is listed as one of the "substances added directly to human food affirmed as generally recognized as safe" (GRAS) and are "used in food as nutrient supplements with no limitation other than current good manufacturing practice" (21 CFR Part 184.1(b)(1) and Part 184.1296(b)-(d). "Nutrient supplements" are further defined as "substances which are necessary for the body's nutritional and metabolic processes" (21 CFR Part 170.3(o)(20).

NDA 20-292 was initially submitted on November 12, 1992 and was refused filling on January 4, 1993 primarily due to a number of chemistry, environmental and clinical issues (see Appendix I (pages 8-9). Regarding biopharmaceutic issues, the sponsor's request for a waiver of the Agency's bioavailability requirements was denied (see Appendix I [page 9]). In the "Refuse to File Letter" to the sponsor dated January 8, 1993 (see Appendix I [pages 10-12), the sponsor was informed that meeting the bioavailability requirements with a bioavailability study would be a condition for final NDA approval (see Appendix I [page 12]). Ultimately, it was learned that the sponsor had blood levels of iron and related iron metabolism parameters that would be re-analyzed and submitted to the Agency (see Appendix I [page 20]).

In the re-submitted NDA, the sponsor provided only pooled pre-dose values and 24 ± 4 h mean ($\pm$SE) postdose values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin obtained in Phase II/III clinical studies which utilized two dose levels of FerriSeltz® containing 200 mg Fe^{3+} (n=136) and 400 mg Fe^{3+} (n=133) (see page 3). The adverse events observed in the Phase II/III studies were also provided (see page 5). Submitted along with these data were 55 literature articles on iron absorption, metabolism and toxicity.

In the literature, it is stated that following oral doses of iron formulations, the time of peak iron absorption is usually 2-4 h postdose. Thus, the pooled Phase II/III 24 ± 4 h postdose values of serum iron and the associated iron metabolism parameters submitted by the sponsor were considered inadequate for accurately assessing the possible absorption of iron from the

FerriSeltz® doses administered in the Phase II/III studies. From a biopharmaceutic perspective, it was considered that the new information provided by the sponsor was not sufficient to permit a substantive review of the NDA. Accordingly, the NDA was considered not filable (see Appendix I [page 23]).

It was felt that in order for NDA 20-292 to be acceptable for filing, the sponsor needed to conduct a study/studies ($n \geq 10$ for each study) using the to-be-marketed FerriSeltz® formulation to assess the potential absorption, systemic exposure, metabolism and elimination of the active moiety/iron. It was recommended that the blood sampling scheme for the requested study/studies allow for an accurate assessment of these parameters and that the blood sampling times should include 0, 1, 2, 3, 4, 6, and 12 h postdose. In this regard, HFD-160 stated (i) that the sponsor had not been explicitly informed that the type of study that is being requested would be needed and (ii) that the NDA would be filed and then the sponsor would be required to conduct the requested study/studies prior to NDA approval (see Appendix I [page 23]).

In the proposed package insert, it is recommended that imaging be performed 5-20 min following FerriSeltz® administration. It is also stated that the FerriSeltz® doses of 200 and 400 g Fe^{3+} are equivalent in contrast enhancement except that the 400 mg Fe^{3+} dose provides better contrast in the "**delineation of the stomach wall and jejunum**". Based on the data provided by the sponsor, overall, the FerriSeltz® doses containing 200 mg Fe^{+3} and 400 mg Fe^{3+} were similar in incidence of adverse events. However, the incidence of gastrointestinal tract related adverse events was 70% higher for the 400 mg iron dose.

The submitted pooled pre-dose and 24 ± 4 h mean ($\pm$SE) postdose values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from the Phase II/III clinical studies that utilized the two FerriSeltz® doses containing 200 and 400 mg of iron are considered less than adequate for accurately assessing the possible absorption and disposition of iron. Ideally, the sponsor should have collected more postdose blood samples in the studies to further assess FerriSeltz® absorption and disposition in these clinical studies. However, at both the 200 mg Fe^{3+} and 400 mg Fe^{3+} dose levels, the pooled 24 ± 4 h mean ($\pm$SE) postdose values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from the Phase II/III clinical studies were not significantly higher than the corresponding pre-dose values (page 3). These data suggest that at both FerriSeltz® dose levels, any increase in serum iron and the associated iron metabolism parameters that might have occurred in the time interval between FerriSeltz® administration and 24 ± 4 h postdose might have been rather transient. Given these findings, the single dose indication of FerriSeltz® and the limited systemic availability of orally administered ferric iron reported in the literature (see Appendix 1 [pages 24-25]), it seems reasonable not to ask for studies to further assess the potential absorption, systemic exposure, metabolism and elimination of iron for the proposed package insert doses of FerriSeltz®.

II. SUMMARY OF INFORMATION ON BIOAVAILABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, METABOLISM, DRUG-DRUG INTERACTIONS, ETC.

1. BIOAVAILABILITY: No study was conducted to accurately evaluate the bioavailability of FerriSeltz®. The sponsor provided only pooled pre-dose and 24±4 h mean (±SE), values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from Phase II/III clinical studies which utilized FerriSeltz® doses containing 200 mg Fe^{3+} (n=136) or 400 mg Fe^{3+} (n=133) (Table 1).

Table 1. Dose Group Absolute Differences in Mean Iron Metabolism Parameters: Pooled Phase II/III Studies (statistically significant differences italicized)

Parameter**	FerriSeltz Dose	Means (± S.E.) Pre-	24±4 hr Post-	Change (post - pre)	Within Group p-value*
Serum iron (mcg/dL)	200 mg Fe	76.5 (3.97)	78.8 (4.11)	1.17 (2.69)	0.663
	400 mg Fe	78.4 (4.13)	78.8 (4.58)	0.71 (3.46)	0.839
TIBC (mcg/dL)	*200 mg Fe*	*327.3 (6.35)*	*320.3 (5.84)*	*-6.58 (3.25)*	*0.045*
	400 mg Fe	*317.2 (6.46)*	*306.1 (6.94)*	*-9.72 (3.73)*	*0.010*
Ferritin (ng/mL)	200 mg Fe	276.1 (37.83)	270.9 (36.62)	-1.28 (7.91)	0.866
	400 mg Fe	452.7 (84.36)	428.0 (68.32)	-32.06 (24.48)	0.193
% Saturation	200 mg Fe	24.3 (1.41)	25.6 (1.48)	0.87 (0.87)	0.319
	400 mg Fe	25.7 (1.54)	26.2 (1.61)	1.04 (1.21)	0.390
Transferrin (mg/dL)	*200 mg Fe*	*238.5 (5.75)*	*282.3 (5.56)*	*-5.64 (2.06)*	*0.007*
	400 mg Fe	*277.9 (6.07)*	*268.3 (6.14)*	*-7.96 (2.34)*	*<0.001*

* Comparison of the change from pre- to post-contrast using paired t-test

** Normal ranges for SmithKline Beecham Labs:

serum iron	50 - 200 mcg/dL (M): 35 - 200 mcg/dL (F)
TIBC	250 - 425 mcg/dL
ferritin	15 - 445 ng/mL (M): 6 - 270 ng/mL (F)
% saturation	20 - 55%
transferrin	214 - 370 mg/dL

Based on literature information, peak absorption of iron from oral iron formulations usually occurs 2-4 h postdose. Therefore, the pooled Phase II/III 24±4 h postdose values of serum iron and the associated iron metabolism parameters were considered less than accurate for assessing the possible absorption and disposition of iron from the FerriSeltz® doses administered in the Phase II/III studies. However, at both dose levels, the pooled 24±4 h mean (±SE) postdose values of serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from the Phase II/III clinical studies were not significantly higher than the corresponding pre-dose values. For some of the iron metabolism parameters, the 24±4 h postdose values were even significantly lower than pre-dose values. These data suggest that at both FerriSeltz® dose levels, any increase in serum iron and the associated iron metabolism parameters that might have occurred in the time interval between FerriSeltz® administration and 24±4 h postdose might have been rather transient.

2. DISTRIBUTION AND METABOLISM: No study was conducted to evaluate the distribution and metabolism of FerrisSeltz®. However, based on literature information, it appears that iron, if absorbed from Ferriseltz®, would undergo the same distribution and metabolic processes as the iron from other oral iron formulations or dietary sources. On this premise, it is reasonable to assume that some of it would enter the hematopoietic pathway and would be incorporated into the hemoglobin of the red blood cells.

The remaining portion would be incorporated into ferritin for storage.

3. ELIMINATION: It appears that unabsorbed iron in FerriSeltz® is eliminated in feces. The amount of iron absorbed from an oral iron formulation depends largely on the iron need of the body. Therefore, once absorbed into the blood, iron is highly conserved. Only about 10% of the body's iron store is lost per year (1 mg per day) in normal adult males. Iron is excreted from the gastrointestinal tract in extravasated red cells. It is also eliminated in bile and in exfoliated mucosal cells. Small amounts of iron are lost in the urine and in desquamated skin. Additional iron loss occurs in menstruating females.

4. PLASMA PROTEIN BINDING: No study was conducted to evaluate the plasma protein binding of FerriSeltz®.

5. FOOD EFFECT: In the package insert, it is stated that FerriSeltz® should be administered under fasted conditions. The effect of food on the disposition of FerriSeltz® has not been studied.

6. SPECIAL POPULATIONS: (a) **Patients with Impaired Bowel**: Studies have not been conducted to assess the disposition of FerriSeltz® in patients with impaired bowel. In the proposed package insert, it is stated that FerriSeltz® "is contraindicated in patients with known or suspected complete bowel obstruction or perforation of the bowel".

(b) **Patients with Iron Overload**: Studies have not been conducted to assess the disposition of FerriSeltz® in patients with iron overload. In the propose package insert, there is no statement of caution or contraindication related to this patient population.

(c) **Pediatric Patients**: Studies have not been conducted to assess the disposition of FerriSeltz® in pediatric patients. In the proposed package insert, it is stated that "safety and effectiveness of FerriSeltz® in children under 18 years of age have not been established".

7. DRUG-DRUG INTERACTIONS: Drug-drug interaction studies with FerriSeltz® have not been conducted. However, based on literature information, iron absorption from the gastrointestinal tract may be enhanced by organic acids such as ascorbic acid, citric acid, and tartaric acid and may be inhibited by complexing agents such as oxalates, phosphates, carbonates, polyphenols, tannins and some antacids that contain carbonate. This information is provided in the proposed package insert under the sub-heading of Drug-Drug Interactions.

8. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONS: FerriSeltz® is administered for local effect in the gastrointestinal tract. In the proposed package insert, it is recommended that imaging be performed 5-20 min postdose. No information was provided as to whether or not there are differences in the quality of contrast for the images obtained at different times within the specified time window. However, it appears that the imaging time window is the time that optimal gastrointestinal tract distension is attained following FerriSeltz® administration. In the proposed package insert, the sponsor also states the following: "**The improvement in delineation of the stomach wall and jejunum was significantly greater with the higher dose compared to the lower dose; otherwise, the two doses showed equivalent improvement**". However, there is no statement that the higher dose (400 mg Fe^{3+}) is proposed only for MRI procedures involving the stomach wall and the jejunum. Based on the data provided by the sponsor (Table 2), overall, the FerriSeltz® doses containing 200 mg Fe^{+3} and 400 mg Fe^{3+} were similar in incidence of adverse events. However, the incidence of gastrointestinal tract related adverse events were 70% higher for the 400 mg iron dose.

Table 2. Incidence of Adverse Events by Body System:
Pooled Phase II/III Studies
(number of patients with event**, excluding laboratory parameters)

	Total Adverse Events			Moderate or Severe Events***		
Event Severity	200mg Fe (6g OMR)	400mg Fe (12g OMR)	Between Group p-value*	200mg Fe (6g OMR)	400mg Fe (12g OMR)	Between Group p-value*
Patients Assessed	136	133		136	133	
Patients with AE	35 (26%)	49 (37%)	0.065	13 (10%)	15 (11%)	0.693
Adverse Events by Body System:						
Body as Whole:	8 (6%)	9 (7%)	0.807	3 (2%)	2 (2%)	1.000
— fever	-0-	1 (1%)		-0-	1 (1%)	
— headache	5 (4%)	5 (4%)		1 (1%)	1 (1%)	
— pain	3 (2%)	3 (2%)		2 (1%)	-0-	
Cardiovascular:	2 (1%)	2 (2%)	1.000	-0-	1 (1%)	0.494
— hypotension	1 (1%)	-0-		-0-	-0-	
— sickle crisis	-0-	1 (1%)		-0-	1 (1%)	
— tachycardia	2 (1%)	1 (1%)		-0-	-0-	
Digestive:	27 (20%)	46 (35%)	0.089	9 (7%)	11 (8%)	0.648
— constipation	3 (2%)	-0-		1 (1%)	-0-	
— diarrhea	14 (10%)	36 (27%)		4 (3%)	7 (5%)	
— dyspepsia	1 (1%)	-0-		-0-	-0-	
— flatulence	1 (1%)	1 (1%)		-0-	-0-	
— nausea	6 (4%)	9 (7%)		2 (1%)	3 (2%)	
— pain, abdominal	4 (3%)	10 (8%)		2 (1%)	3 (2%)	
— pain, rectal	-0-	1 (1%)		-0-	1 (1%)	
— vomiting	3 (2%)	3 (2%)		1 (1%)	2 (2%)	
Nervous system:	3 (2%)	-0-	0.247	3 (2%)	-0-	0.247
— anxiety	1 (1%)	-0-		1 (1%)	-0-	
— convulsion s	1 (1%)	-0-		1 (1%)	-0-	
— insomnia	2 (1%)	-0-		2 (1%)	-0-	
Respiratory system:	1 (1%)	2 (2%)	0.619	-0-	1 (1%)	0.494
— coughing	-0-	1 (1%)		-0-	1 (1%)	
— epistaxis	1 (1%)	-0-		-0-	-0-	
— rhinitis	-0-	1 (1%)		-0-	-0-	
Skin:	-0-	1 (1%)	0.494	-0-	-0-	
— pruritis	-0-	1(1%)		-0-	-0-	
Urogenital system:	1 (1%)	1 (1%)	1.000	-0-	-0-	
— dysmenorrhea	1 (1%)	-0-		-0-	-0-	
— infection (UTI)	-0-	1 (1%)		-0-	-0-	

* Based on Fisher's Exact test (two-tailed)
** A patient may appear more than once within a body system
***Toxicity grade 2, 3, or 4

BEST POSSIBLE COPY

9. FORMULATION: The composition of FerriSeltz® is presented below.

COMPOSITION AND DOSAGE FORM

FerriSeltz™ is formulated as a powder that readily dissolves in water to create a grape-flavored effervescent drink. The composition is as follows:

Ingredient	mg/packet
Ferric ammonium citrate, brown	600
Sodium bicarbonate, USP	1250
Tartaric acid, NF	1100
Aspartame, NF	47
Flavor- Grape Micron ZD-3870	3
Total	3000 mg

III LABELING COMMENTS

1. In the proposed package insert, it is stated that "**safety and effectiveness of FerriSeltz® in children under 18 years of age have not been established**". Therefore, for the **Indication and Usage** section of the proposed package insert, the following might be considered:

> FerriSeltz™ is an oral contrast agent for marking the upper gastrointestinal tract in **adult** patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen.

2. Will FerriSeltz® be used in patients with iron overload (i.e., patients with hemochromatosis and hemosiderosis)? If so, a statement related to the possible risks needs to be included in the package insert. If not, an explicit statement of contraindication should be included in the package insert.

3. In the proposed package insert, the following is stated: "**The improvement in delineation of the stomach wall and jejunum was significantly greater with the higher dose compared to the lower dose; otherwise, the two doses showed equivalent improvement**". Why is the higher dose (400 mg Fe^{3+}) not recommended only for MRI procedures involving these two organs (i.e., stomach wall and jejunum)?

IV. RECOMMENDATION

NDA 20-292, which was re-submitted by the sponsor for ferric ammonium citrate, brown (FerriSeltz®) on November 15, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. Based on the information that is provided, from a clinical pharmacology/pharmacokinetic perspective, the NDA is considered approvable. The General Comment (page 6) should be brought to the attention of the reviewing medical officer. Labeling Comments 1, 2 and 3 (page 6) should also be brought to the attention of reviewing medical officer in order to assess if they have merit for inclusion in the package insert.

Please convey this Recommendation, as appropriate, to the sponsor. Labeling Comments 1, 2 and 3 (page 6) should also be conveyed to the sponsor, as appropriate, if the medical officer concurs.

Appendix I is retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

APPEARS THIS WAY
ON ORIGINAL

10/25/96
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt 10/17/96

FT Initialed by John Hunt 10/25/96

Clinpharm/Biopharm Briefing: 25/10/96 at 9.00 a.m in PKLN Room 11-61 (Attendees: Malinowzki (HFD-860), Lazor (HFD-880), Hunt (HFD-860), Jones (HFD-160), Raczkowski (HFD-160), Chow (HFD-160) and Arnstein (HFD-160).

cc: NDA 20-292, HFD-160, HFD-870 (M. Chen, Hunt, and Udo), HFD-870 (Drug, Chron, Reviewer [Clarence Bott, PKLN Rm. 13B-31]), HFD-340 (Viswanathan).

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

ADMINISTRATIVE DOCUMENTS

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Acting Commissioner of Patents and Trademarks

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United States Patent [19]

Takaichi et al.

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[45] Date of Patent: Dec. 29, 1992

[54] METHOD OF USING IRON CONTAINING PREPARATION FOR NMR IMAGING

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[51] Int. Cl.[5] G01N 24/00; G01N 31/00; A61L 9/04; A61K 33/00

[52] U.S. Cl. 424/9; 424/44; 424/647; 424/648; 424/700; 424/715; 424/717; 436/173; 128/653.4

[58] Field of Search ..... 424/9, 646, 647, 648, 424/44, 715, 717, 700; 436/173; 128/653 AF, 654

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[57] ABSTRACT

There is described an iron containing preparation for NMR imaging comprising, as necessary ingredients, the prescribed amounts of an iron containing compound, sodium carbonate or sodium hydrogencarbonate and a neutralizing agent. This preparation is safe, easy to drink, and when taking, provides clear and accurate contrast imaging of inner organs. Further, addition of potassium carbonate to this preparation gives excellent preservation stability.

24 Claims, 5 Drawing Sheets

FIG. 1

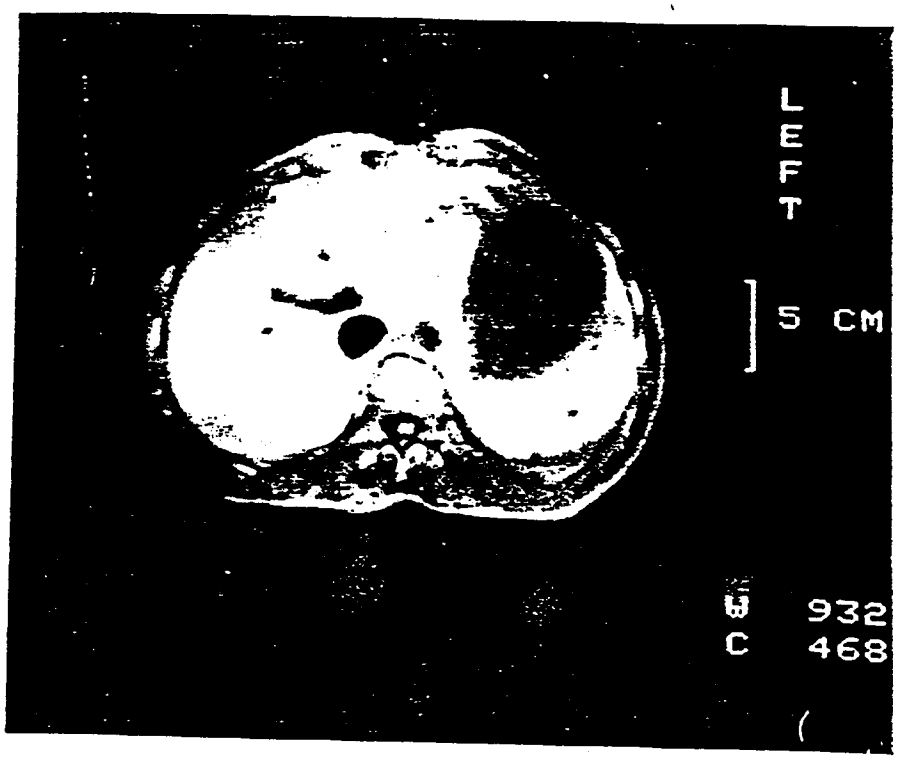


FIG. 2

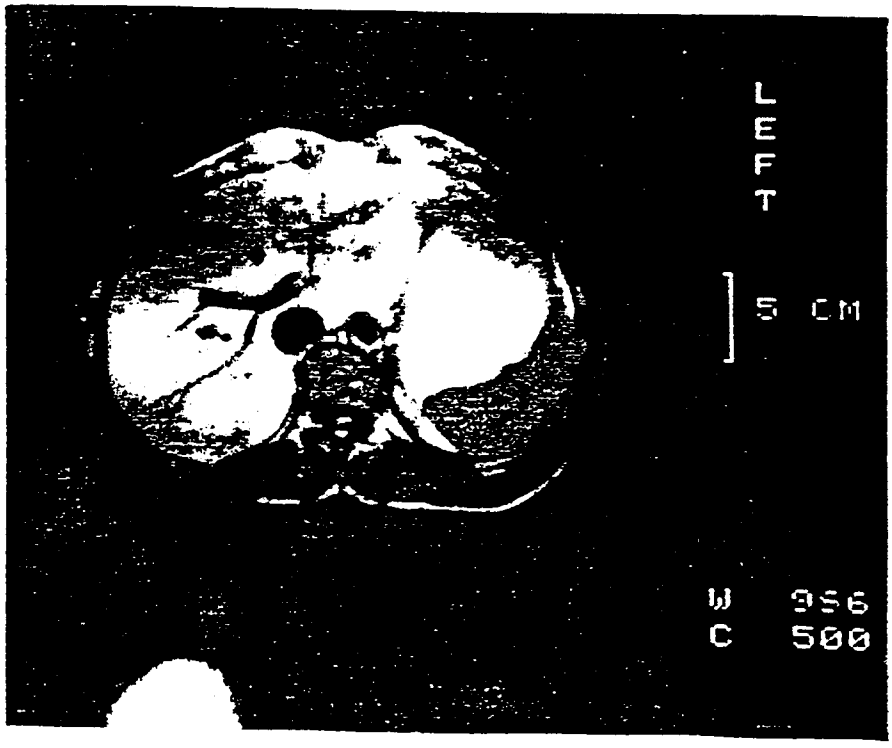


FIG. 3

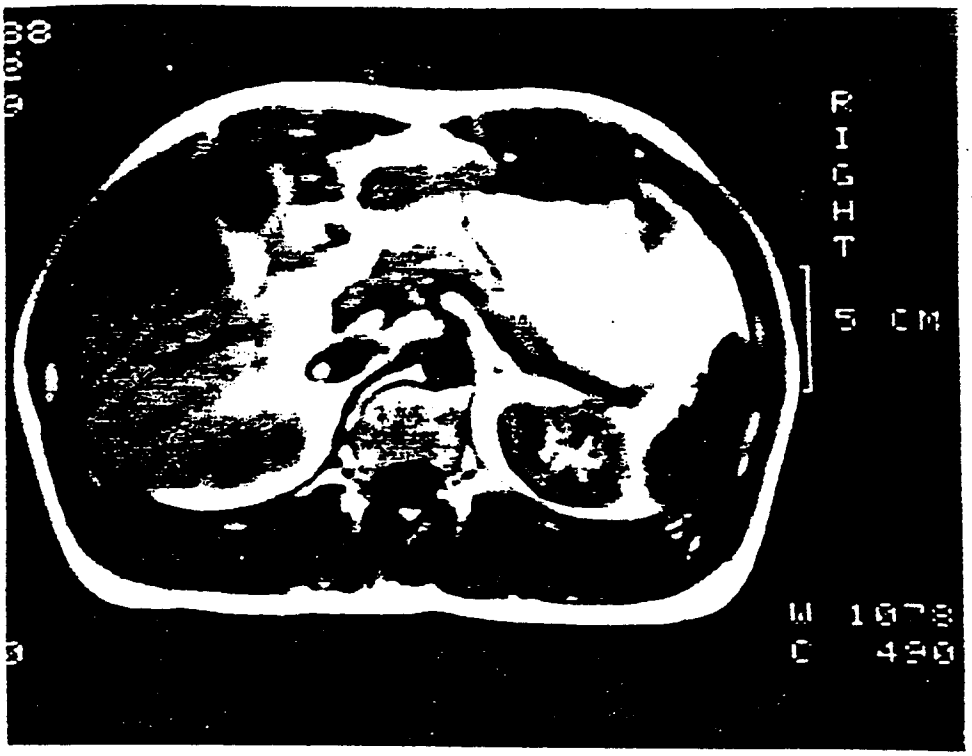


FIG. 4

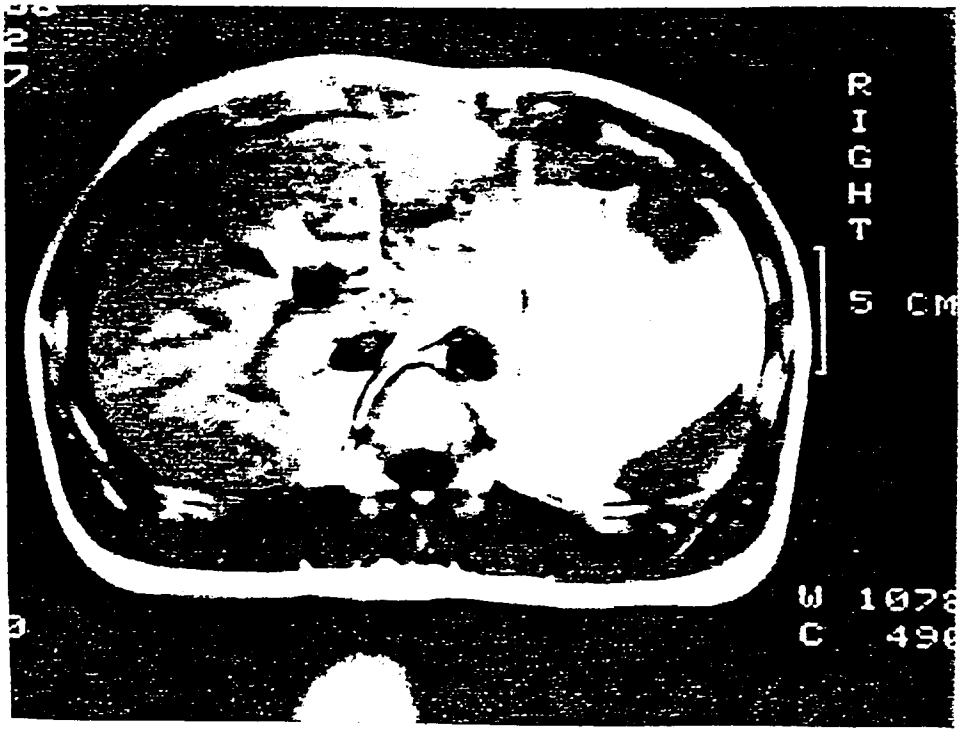


FIG. 5

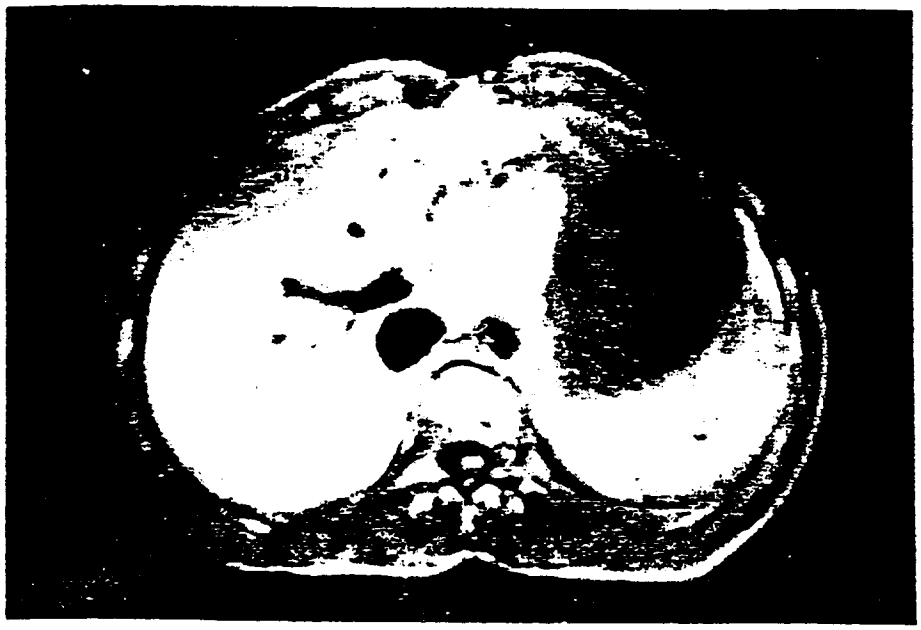


FIG. 6

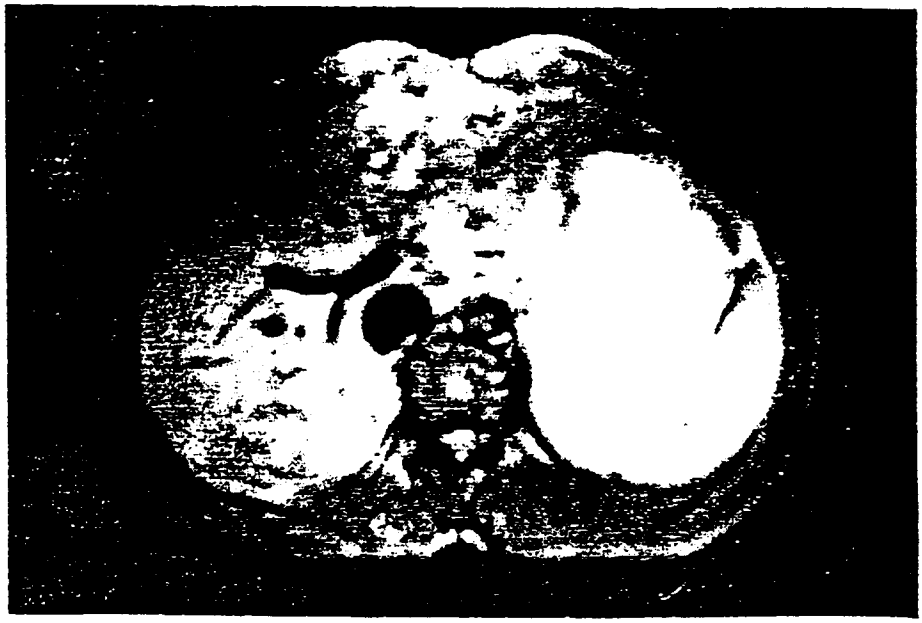


FIG. 7

FIG. 8

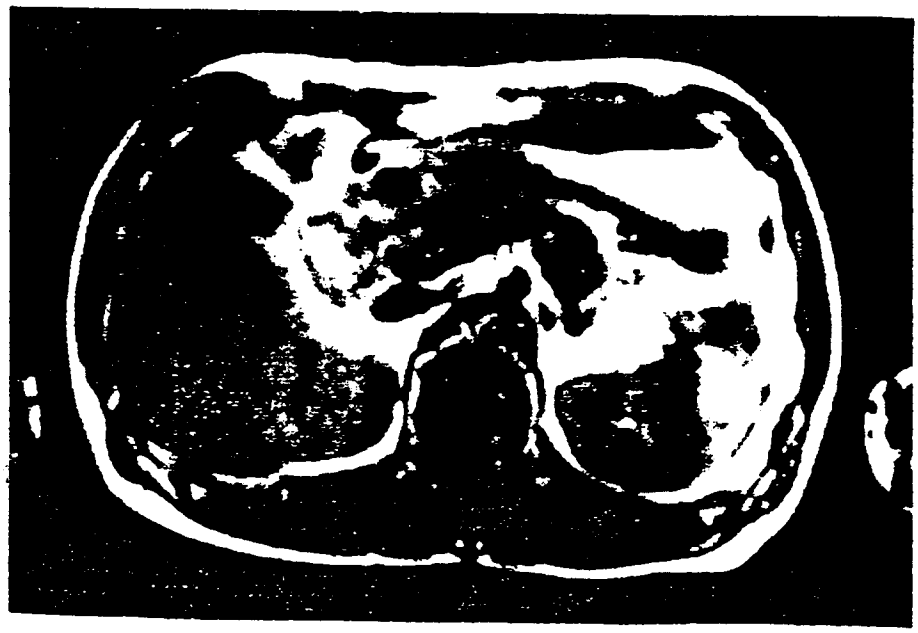
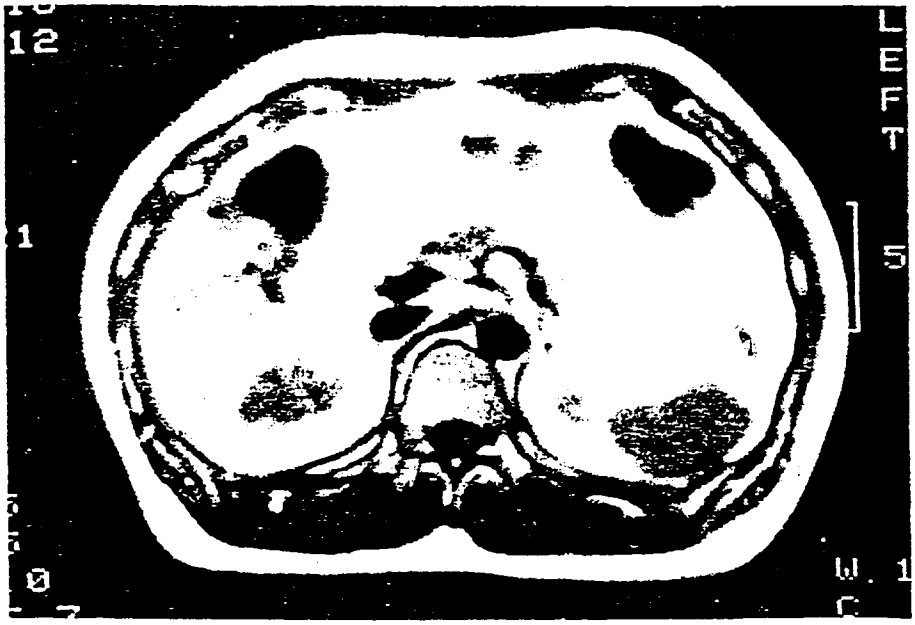


FIG. 9



METHOD OF USING IRON CONTAINING PREPARATION FOR NMR IMAGING

TECHNICAL FIELD

This invention relates to a iron containing preparation for NMR imaging and to an NMR imaging method using the same, which preparation has a form such as a foaming tablet, powder or the like.

BACKGROUND OF THE INVENTION

Since the beginning of 1970, NMR (Nuclear Magnetic Resonance) is widely utilized as a medical diagnostic apparatus, especially as an imaging means capable of providing soft organization imagings having high resolution and contrast without using detrimental x-ray.

That is to say, many atoms have a certain property called as spin to which small magnetic moment is attached.

When the outer magnetic field does not exist, configuration of a magnetic moment is irregular, but in the presence of static magnetic field, nuclear magnetic moment takes precession to approximately the magnetic field direction, so that net alignment is generated in the magnetic field. NMR imaging method is achieved by using this priciple. According to NMR imgaging method, when a short radio frequency pulse is oscillated from a coil surrounding a patient which is set in a static magnetic field, a configuration based on the new magnetic field and precession in phase are generated by this pulse. On the other hand, when oscillation of the pulse is stopped, the above moment returns to the distribution of alignment and the irregular distribution of precession phase on the basis of the former static magnetic field. In such a case, detectable nuclear magnetic resonance is generated at the receiving coil, and by measuring such NMR signals, a proton density map of the objective tissue can be represented. Also, the NMR signal is largely depended with parameters of spin-lattice relaxation time (T_1, i.e. the time specific to return of nuclear magnetic moment to balance alignment in static magnetic field) and spin-spin relaxation time (T_2, i.e. the time specific to return the nuclear magnetic moment to the irregular precession phase distribution). Therefore, these mesurements can be applied to the diagnosis of pathogenic tissue states of a patient.

In NMR imaging method, it is known that physical parameters such as temperature, viscosity and hydration or the like of the tissue is effective to increase NMR signal strength or to change the contrast an NMR image. However, these methods are apparently not suitable for clinical applications. A method for enhancing the contrast of NMR images which is known in the present stage using a paramagnetic compound, as a contrast agent, which decreases spin-lattice relaxation time (T_1) at low concentration thereof, and decreases spin-spin relaxation time (T_2) at high concentration thereof. Contrast agents have been researched, and a typical example of such contrast agents are inorganic paramagnetic salts such as iron, manganese, chromium; or a organic chelate complex which consists of the paramagnetic metal ion mentioned above and one of various complex forming agents which are usually are aminopolycarbxylic acid such as ethylenediaminetetraacetic acid or diethy lenetriaminepentaacetic acid. The contrast agent is taken orally or otherwise in the form of a solution or a colloidal dispention liquid.

However, all of the known contrast agents which are suggested are found to be insufficient practically for use in NMR imaging methods, e.g., due to the difficulty in preparing such agents in a pharmaceutically acceptable form, a lack stability of the pharmaceutical form, difficulties in oral administration, poor taste, toxicity, or the like and, and ineffective viewing for using as a contrast agent, e.g. due to accuracy, clearness.

SUMMARY OF THE INVENTION

A object of the invention is to provide an iron containing preparation for NMR imaging, which is easily prepared in pharmaceutically acceptable form, and which has excellent solubility or dispersion in water so as to rapidly and easily dissolve or disperse in water, thereby being suitable for oral administration.

Another object of the present invention of the invention is to provide an iron containing preparation for NMR imaging, which has excellent storage stability.

Another object of the present invention of the invention is to provide an iron containing preparation for NMR imaging which is capable of accurately and clearly imaging abdominal organs by use as a contrast agent, and NMR imaging method using such a preparation.

According to this invention, there is provided an iron containing preparation for NMR imaging comprising, as essential ingredients, 0.1 to 10% by weight, as elemental iron, of an iron containing compound, 8 to 60% by weight of one or both selected from sodium carbonate and sodium hydrogen carbonate and 10 to 70% by weight of neutralizing agents.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A preparation of this invention can be used in the form of tablet, granule, powder or capsule.

A preparation of this invention, especially in the form of powder or tablets, as excellent dissolution or dispersion properties in water. Therefore, an iron containing compound contained is easily dissolved or dispersed in water by merely putting the preparation into water, which generate carbonic acid gas (carbon dioxide) due to neutralization. Accordingly, a preparation is easily taken orally. Also, carbonic acid gas generated in the body of the patient makes the alimentary canal expand and extend, so that the form of alimentary canal, the state of lumen thereof and the relation between alimentary canal and other surrounding internal organs can be easily accomplished.

Furthermore, by taking a preparation of this invention, an extremely significant effect occurs such that signal strength of lumen of alimentary canal is enhanced so that imaging of the alimentary canal wall with enhanced contrast against adjacent abdominal organs such as pancreas and the like is achieved.

In addition, each ingredient in preparations of this invention is a safe material having low toxicity.

According to this invention, in order to improve preservation stability, there is provided iron containing preparations for NMR imaging comprising the above iron containing compound, and at least one of sodium carbonate and sodium hydrogen carbonate, the neutralizing agent and potassium carbonate as a preservation stabilizing agent.

Addition of potassium carbonate overcomes a disadvantage found in conventional foam preparations, i.e. foam or degeneration of product during preservation

due to the existence of residual water resulting from the manufacturing process or hydration.

Examples of the iron containing compounds preferably employed in this invention are ammonium iron(II) citrate, ammonium iron(III) citrate, sodium iron(II) citrate, sodium iron(III) citrate, iron(II) citrate, iron-(III) citrate, iron(II) gluconate, iron(II) pyrophosphate, iron(III) pyrophosphate, iron lactate, iron(II) sulfate, iron(III) chloride, iron sesquioxide, sodium iron chlorophyn, iron(II) fumarate, iron threonine, iron(II) orotinate, saccharated iron oxide, iron(III) gluconate or the like. These iron containing compounds are excellent in soluble and dispersive properties in water. These iron containing compounds are also used as an active component of a therapeutic agents for iron deficiency anemia, deficiency anemia, hematinic iron agent or the like in pharmaceutical field, and have high safety. In the iron containing compounds mentioned above, it is preferred to use trivalent iron salt, and especially it is most preferred to use trivalent citrate type, in view of safety and enhanced imaging (on contrast) effects, good taste and ease of drinking.

The iron containing compound is added in the form of a powder, the diameter of particles of which is ordinally not more than 200 μm. Each iron containing compound may be used alone or as a mixture of 2 or more kinds thereof. The amount of iron containing compound to be added is 0.1 to 10% by weight, preferably 0.5 to 5% by weight as elemental iron. Within this amount, the preparation of this invention achieves accurate and clear contrast effects in NMR imaging. This amount corresponds with about 10 to 300 mg, preferably about 25 to 100 mg per one preparation of the foam preparation of this invention.

At least one of sodium carbonate and sodium hydrogen carbon and a neutralizing agent are added as a foaming component, together with the above iron containing compound. The term neutralizing agent 11 means an acid compound capable of neutralizing sodium hydrogen carbonate and sodium bicarbonate to generate carbonic acid gas. Such a foam has the function of expanding and extending the alimentary canal, and therefore is very advantageous to know the form of alimentary canal and the state of its lumen from an NMR picture. Examples of such neutralizing agents are organic acids such as L-tartaric acid, citric acid, fumaric acid, lactic acid, malic acid or ascorbic acid, and it is especially preferred to use L-tartaric acid and/or citric acid.

The amount of the above foam component to be blended is provided such that the solution obtained by dissolving in water that is acidic, especially at a pH of about 3 to 5.5 of pH, preferably about 3.5 to 4.6 of pH, whereby the iron containing compound is rapidly dissolved in water. In particular, for example, the blending amount of each ingredient, sodium carbonate and/or sodium hydrogencarbonate is 8 to 60% by weight, and the neutralizing agent is 10 to 70% by weight. In the case where the preparation of this invention is used in the form of powder or the like, when the amount of sodium carbonate and/or sodium hydrogencarbonate is 20 to 60% by weight, excellent imaging effect is obtained, and when the amount of sodium carbonate and/or sodium hydrogen carbonate is 8 to 45% by weight, taste is improved so as to be agreeable to drink. Practically, it is therefore desirable for providing good taste and to facilitate admistration together with high imaging effect, that sodium carbonate is added at 9 to 50% by weight, preferably 22 to 26% by weight, and that sodium hydrogen carbonate is 8 to 50% by weight, preferably 20 to 45% by weight.

It is suitable that the neutralizing agent is added in the range of 20 to 50% by weight, preferably 30 to 40% by weight, and especially it is preferable to use at the same amount as or more than the equivalent amounts of sodium hydrogen carbonate.

According to this invention, in addition to sodium carbonate and/or sodium hydrogencarbonate and a neutralizing agent added as a foam component, it is preferred that potassium carbonate is added as a preservation stabilizing agent. That is to say, since sodium carbonate or sodium hydrogen carbonate are neutralized in the presence of water by a agent such as organic acid to generate carbonic acid gas and to promote the degradation and dissolution of the preparation, the preparation should be kept in a dry condition as much as possible so as to prevent foaming. There, however, a possibility of foaming during storage due to the presence of water remaining in preparing process or as hydration, even if it is preserved in a sealed container together with drying agent. If carbonic acid gas is generated during preservation, inner pressure of the sealed container is increased, and results in deformation or damage of the container, or can inhibit foaming when the product is used. Foaming during preservation is accelerated under a high temperature condition, and further the generated reaction water and carbonic acid gas accelerate the reaction.

It is now found that potassium carbonate is very effective to prevent foaming during preservation as mentioned above, and even if drying agent is not used during storage, foaming can be prevented. In view of securing a high stability of the preparation and easily taking it without lowering taste, it is suitable that potassium carbonate is added at the amount of 0.2 to 13% by weight, preferably 0.3 to 3% by weight, more preferably 0.4 to 1% by weight per one preparation.

Potassium carbonate used in this invention is not particular limited, and it is especially preferred to use one having no hydration, such as potassium carbonate anhydride.

To a preparation of this invention, if necessary, various additives ordinally known, such as a vehicle, binding agent, disintegrator, lubricant, thickener, surface active agent, osmotic pressure adjusting agent, electrolyte, sweetening agent, perfume, coloring matter, pH adjusting agent or the like, can be added, in addition to the above iron containing compound and foam components. Examples of vehicles are starches such as wheat starch, potato starch, corn starch, dextrin; saccharides such as sucrose, glucose, fructose, maltose, xylulose, lactose or the like; sugar alcohols such as sorbitol, mannitol, maltitol, xylitol or the like; saccharide-transglycoside such as coupling sugar, palathinose or the like; calcium phosphate; calcium sulfate; or the like. Examples of the binding agents or thickeners are starch, saccharides, gelatin, gum arabic, dextrin, methyl cellulose, CMC-Na, polyvinyl pyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, xanthan gum, pectin, tragacanth gum, casein, alginic acid, or the like. Examples of lubricants are leucine, isoleucine, L-valine, sugar-ester, hardened oil, stearic acid, magnesium stearate, talc, macrogol or the like. Examples of disintegrators are avicel, CMC, CMC-Ca or the like. Example of surface active agents are polysorbate, lecithin or the like. Examples of sweetening agents are saccharides; sugar alco-

hols: dipeptides such as aspartame, alitame; stevia; saccharin; or the like.

The suitable amounts of these additives can be determined in view of the relationship between the additives and the essential ingredients, properties of preparation, process for preparing it or the like.

Furthermore, the suitable amount of various vitamines, especially cyanocobalamin, ascorbic acid (vitamine C) or the like, may be added to the preparation. Therefore, it also is possible to supply vitamin to the body. The amount of the vitamin to be added is not limited, and vitamine C may be added at an amount of not exceeding 30% by weight, preferably about 5 to 25% by weight in view of taste.

A preparation of this invention can be not only in the form of a tablet, but also may be in other solid forms such as granule, powder, capsule or the like.

In preparing a preparation of this invention, methods similar to conventional methods employed in respective preparation form may be employed. For example, a tablet form can be prepared by a method for directly pressurizing powders or by a method for dry or wet pressurizing granules, after weighing and mixing the prescribed amount of each ingredient. Also, powder can be prepared by weighing and mixing the prescribed amount of each ingredient followed by folding. Granules can be prepared by drying to form particles followed by folding, after weighing and mixing the prescribed amount of each ingredient.

A preparation of this invention which is in the form of foam tablet or powder is put into water to dissolve or disperse, and then is orally taken. Conversely, the preparation of this invention may be orally taken in its unchanged form followed by drinking water.

Dosage of a preparation of this invention should be calculatec by known methods based on which internal organ or organization of the living body is to be imaged, and in general, may be taken by dissolving 1.5 to 6 g of the preparation in 100 to 300 ml of water. In the case of contrast imaging of pancreas, 1 or 2 tablets which are prepared at about 1.5 to 6 g per one tablet are taken by dissolving in 100 to 300 ml of water.

A preparation of this invention can be utilized in NMR diagnosis of the alimentary canal, i.e. walls of alimentary canal such as stomach, duodenum, small intestine, large intestine or the like; or pancreas, liver, peritoneum, mesentery or a like. In this case, the preparation of this invention is suitable to contrast imaging representation between alimentary canal and parenchymal internal organs, whereby T_1 value is shortened.

BRIEF EXPLANATION OF THE DRAWINGS

FIG. 1 is a NMR imaging photograph of abdominal part before taking the preparation of Example 1;

FIG. 2 is a NMR imaging photograph of abdominal part after taking the preparation of Example 1;

FIGS. 3 and 4 are NMR imaging photographs of abdominal part of the other subject after taking the preparation of Example 1;

FIG. 5 is a NMR imaging photograph of abdominal part before taking the preparation of Example 20;

FIG. 6 is a NMR imaging photograph of abdominal part of the other subject after taking the preparation of Example 20;

FIGS. 7 to 9 are NMR imaging photographs of abdominal part of the other subject after taking the preparation of Example 20.

INDUSTRIAL APPLICABILITY

As mentioned above, a preparation of this invention makes it possible to take it orally with ease, and to expand and extend alimentary canal by foaming of the foaming ingredients. As a result, form of alimentary canal, the state of its lumen and the relationship between alimentary canal and the surrounding organs can be easily known. Furthermore, a preparation of this invention has an excellent imaging effect enhancing signal strength in the alimentary canal. Thus, it is expected to improve the accuracy of diagnosis of various diseases.

Also, by adding potassium carbonate to the foam preparation, foaming and altertion during preservation can be prevented, and as a result, the preparation of this invention is superior in preservation stability.

EXAMPLES

Examples of this invention are explained below in detail. In each example, "parts" and "%" mean "parts by weight" and "% by weight", respectively, except as otherwise indicated.

EXAMPLE 1

After mixing each ingredient at the ratio shown below, foam tablets (4.3 g per one tablet) were pharmaceutically prepared from the mixture by a method for directly pressurizing powder.

(Ingredients)	(%)
Granulated sugar	37
L-Ascorbic acid	12
L-Tartaric acid	22
Apartame	0.8
Sodium hydrogencarbonate	23
Ammonium iron citrate (25 mg/4.3 g as elemental iron)	3.4
Cyanocobalamin	trace amount
perfume and coloring	proper amount
Total	100

EXAMPLES 2 to 8

Foam tablets having compositions shown in Table 1 was prepared by the same method as Example 1.

TABLE 1

Ingredients		Example No. 2	3	4	5	6	7	8
Glanulated sugar	(parts)	34	30	26	14	17	39	28
L-Ascorbic acid	(parts)	12	12	12	16	16	12	12
L-Tartaric acid	(parts)	22	22	22	30	30	23	27
Aspartame	(parts)	0.8	0.8	0.8	1.0	1.0	0.8	0.8
$NaHCO_3$	(parts)	23	23	23	31	31	20	25
Ammonium iron citrate	(parts)	6.8	10.2	14	6.8	3.4	3.4	6.8
Cyanocobalamin	(parts)	*	*	*	*	*	*	*
Perfume and coloring	(parts)	**	**	**	**	**	**	**
Preparation weight (g/one tablet)		4.3	4.3	4.3	4.3	4.3	4.3	4.3

TABLE 1-continued

Ingredients	Example No. 2	3	4	5	6	7	8
Iron content/one tablet (mg)	50	75	100	50	25	25	50

*indicates "a trace amount of cyanocobalamin"
**indicates "a suitable amount of perfume and coloring matter"

EXAMPLES 9 TO 20

The prescribed amount of each ingredient shown in Table 2 was weighed and mixed, and further sweetening agent and perfume are added at suitable amounts. Then, by folding the mixture, foam powders having a weight (mg/one package) shown in the same table were prepared.

TABLE 2

Ingredients	Example No. 9	10	11	12	13	14	15	16	17	18	19	20
L-Tartaric acid (mg)	893	893	893	893	893	447	1786	893	893	447	1786	1100
$NaHCO_3$ (mg)	1000	1000	1000	1000	1000	500	2000	500	2000	1000	1000	1250
Ammonium iron citrate (mg)	60	150	300	600	1200	600	600	600	600	600	600	600
Total (mg/one package)	1953	2043	2193	2493	3093	1547	4386	1993	3493	2047	3386	2950
Iron content/ one package (mg)	10	25	50	100	200	100	100	100	100	100	100	100

It was also recognized that foam tablets obtained in Examples 2 to 11 show the same enhancement as that of each subject number at the same dose of iron as the above test. Accordingly, a foam tablet obtained in each Example can be suitably applied to abdominal diagnosis using NMR.

These test results were confirmed by administering to subjects the foam tablet obtained in each Example and taking photographs of abdominal image. That is, as shown in FIG. 1 which is T_1 enhancement image of an abdominal part of subject No. 4 before taking, since the inner part of stomach is filled by water and signal is weak, the inner part of stomach is represented by gray or black color, and it is hard to distinguish alimentary canal from other adjacent organs. On the other hand, as shown in FIG. 2 which is T_1 enhancement image after taking, time T_1 in stomach is shortened, signal strength is increased, and therefore distinction between alimentary canal and other adjacent organs is clear.

Also, as shown in FIGS. 3 and 4, according to T_1 enhancement images after taking, distinction between the alimentary canal and other adjacent organs is clear. Especially, as shown in FIG. 3, the border between pancreas and other internal organs can be clearly confirmed; the head of pancreas which is otherwise difficult to detect anatomically is apparently recognized; other organs such as lung, tail of pancreas, body of pancreas, liver, ren, blood vessel or the like were also recognized clearly; and further stomach wall was clearly identified.

NMR Imaging Test (I)

1, 1.5, 2 and 2.5 foam tablets (including 25 mg, 37.5 mg, 50 mg and 62.5 mg of iron, respectively) prepared in Example 1 were taken to four healthy and ordinary subjects (Nos. 1 to 4) by dissolving in 140 ml of water respectively. NMR imaging is carried out before and after taking foam tablets. In such a case, photographs of T_1 enhancement image (SE 500 to 600/17 m sec.) and T_2 enhancement image (SE 2000/23.90 m sec.) were taken. T_1 and T_2 values were measured from images of SE 500/23 and 2000/23.90 by double point method. Also, as a mesurment equipment, 1.5T MRI (Magnetom) manufactured by Siemens, W. Germany, and 8 to 10 mm of slice thickness and 4 to 5 mm of slice interval were set.

T_1 and T_2 values in stomach which were obtained by the above test are shown in Table 3.

TABLE 3

Subject No.	Dose (mg of iron)	Before taking (Stomach) T_1/T_2	After taking (Stomach) T_1/T_2
1	25.0	3111/122	2213/149
2	37.5	3635/193	744/179
3	50.0	2379/178	573/272
4	62.5	3305/202	565/307

The following matter becomes apparent from Table 3. Enhancement of liquid contained in stomach is recognized at all of four doses. Especially, when dose is 25 mg and 62.5 mg of iron, enhancement of liquid contained in stomach is remarkable, and images of stomach wall and pancreas, especially head of pancreas become clear. As to the degree of enhancement, when dose is 50 mg of iron, signal strength of the above liquid contained in stomach is slightly less than that of fatty tissue in abdominal cavity, and therefore the above liquid can be distinguished from the above fat.

NMR Imaging Test (II)

One package of the foam powder (including 100 mg of iron) prepared in Example 20 was taken by a healthy and ordinary subject by dissolving in 140 ml of water, and further 150 ml of water was given to the subject. FIGS. 5 and 6 are photographs for imaging abdominal part of the subject before and after taking the foam powder. FIG. 5 is T_1 enhancement image of stomach part in the condition that water was given to expand alimentary canal. As shown in FIG. 5, signal of water is weak, whereby the inner part of stomach is represented by gray or black color, and distinction between wall and lumen of alimentary canal is unclear. Furthermore, it is difficult to recognize distinction between alimentary canal and the adjacent organs such as pancreas, liver, lung, peritoneum or the like.

On the other hand, signal strength in stomach after taking is increased as shown in T_1 enhancement image of FIG. 6, the inner part of stomach is drawn out by white color, and is contrasted to the surrounding organs. Also, as described herein, the stomach wall and the duodenum wall are well recognized, and the tail and head of pancreas are clearly distinguished from the surrounding organs and alimentary canal.

FIG. 7 is T_1 enhancement image after taking one package of foam powder obtained by Example 20 with 300 ml of water. In general, it is difficult to take an image of head of pancreas, since its T_1 signal approximates to that of duodenum. However, by taking the foam powder of this Example, since the duodenum is expanded and extended by generating carbonic acid gas, and signal strength is increased, head of pancreas can be very clearly drawn out. Similarly, the stomach is fully expanded and extended by water and carbonic acid gas, the border between stomach and body of pancreas is distinct, and contrast is enhanced.

It is understood from FIG. 8 that distinction between the wall of duodenum and inner wall is clear, since the duodenum is expanded and extended by generating carbonic acid gas. It is also understood from FIG. 9 that duodenum is expanded and extended from the same reason as FIG. 8.

Accordingly, from the results shown in FIGS. 5 to 9, the form of abdominal organ and relationship between the same and other organs can be accurately and clearly known by taking the foam powder of this Example, whereby it is expected to improve the accuracy of diagnosis against various diseases.

EXAMPLE 21 (including potassium carbonate)

Foam tablet having the composition shown below was prepared by the same manner as Example 1.

(Ingredients)	(%)
Granulated sugar	40
L-Tartaric acid	29
Aspartame	0.8
Sodium hydrogencarbonate	21
Ammonium iron citrate	3.6
Potassium carbonate	0.5
Cyanocobalamin	trace amount
Sweetening agent	proper amount
Perfume and coloring	proper amount
Total	100 (4.0 g)

Stability Test

The foam tablet obtained in Example 21 was stored in a constant temperature room kept at 37° C., together with the comparative foam tablet which was prepared by the same manner as that of Example 21 except for not adding potassium carbonate, and a swelling test (by wrapping sheet) discoloration test of tablets, solubility in water and change of taste were examined with time. As a result, the foam tablet of Example 21, with added potassium carbonate had low swell, little discoloration, shorter dissolving time and less change of taste in comparison with the comparative foam tablet, and therefore is superior to the compartive foam tablet in preservation stability.

What is claimed is:

1. A nuclear magnetic resonance imaging method comprising administering a diagnostically effective amount of a contrast medium to a subject and performing nuclear magnetic resonance tomography on said subject, said contrast medium comprising:

0.1 to 10% by weight, as elemental iron, of at least one iron containing compound selected from the group consisting of an iron (II) salt and an iron (III) salt;

8 to 60% by weight of at least one of sodium carbonate and sodium hydrogen carbonate; and

10 to 70% by weight of a neutralizing agent, wherein said neutralizing agent reacts with said at least one of sodium carbonate and sodium hydrogen carbonate to produce carbon dioxide in the alimentary canal of said subject, when orally administered to the subject with water, and wherein the produced carbon dioxide expands and extends the alimentary canal.

2. A method according to claim 1, wherein said iron containing compound is at least one selected from the group consisting of ammonium iron(II) citrate, ammonium iron(III) citrate, sodium iron(II) citrate, sodium iron(III) citrate, iron(II) citrate, iron(III) citrate, iron(II) gluconate, iron(II) pyrophosphate, iron(II) pyrophosphate, iron lactate, iron(II) sulfate, iron(III) chloride, iron sesquioxide, sodium iron chlorophyn, iron(II) fumarate, iron threonine, iron(II) orotinate, saccharated iron oxide, and iron(III) gluconate.

3. A method according to claim 2, wherein said iron containing compound is a trivalent iron salt.

4. A method according to claim 3, wherein said iron containing compound is a trivalent iron citrate salt.

5. A method according to claim 1, wherein said iron containing compound is present in an amount of 0.5 to 5% by weight as elemental iron.

6. A method according to claim 1, wherein said neutralizing agent is selected from the group consisting of L-tartaric acid, citric acid, fumaric acid, lactic acid, malic acid and ascorbic acid.

7. A method according to claim 6, wherein said neutralizing agent is at least one of tartaric acid and citric acid.

8. A method according to claim 1, wherein said preparation, when dissolved in water, has a pH of 3 to 5.5.

9. A method according to claim 8, wherein the pH is 3.5 to 4.6.

10. A method according to claim 1, wherein said preparation comprises 20 to 60% by weight of said at least one of sodium carbonate and sodium hydrogencarbonate.

11. A method according to claim 10, wherein said preparation comprises 8 to 45% by weight of said at least one of sodium carbonate and sodium hydrogen carbonate.

12. A method according to claim 1, wherein said sodium carbonate is present in an amount of 9 to 50% by weight.

13. A method according to claim 12, wherein said sodium carbonate is present in an amount of 22 to 26% by weight.

14. A method according to claim 1, wherein said sodium hydrogen carbonate is present in an amount of 8 to 50% by weight.

15. A method according to claim 14, wherein said sodium hydrogen carbonate is present in an amount of 20 to 45% by weight.

16. A method according to claim 1, wherein said neutralizing agent is present in an amount of 20 to 50% by weight.

17. A method according to claim 16, wherein said neutralizing agent is present in an amount of 30 to 40% by weight.

18. A method according to claim 1, wherein said preparation is in a form capable of being dissolved or dispersed in water.

19. A method according to claim 18, wherein said preparation is in the form of a foaming powder.

20. A method according to claim 18, wherein said preparation is in the form of a foaming tablet.

21. A nuclear magnetic resonance imaging method comprising administering a diagnostically effective amount of a contrast medium to a subject and performing nuclear magnetic resonance tomography on said subject, said contrast medium comprising:

at least one iron containing compound selected from the group consisting of an iron (II) salt and an iron (III) salt

at least one of sodium carbonate and sodium hydrogen carbonate:

a neutralizing agent, and

potassium carbonate as a preservation stabilizing agent; wherein said neutralizing agent reacts with said sodium carbonate or sodium hydrogen carbonate to produce carbon dioxide in the alimentary canal of a subject, when administered to said subject together with water, and wherein said produced carbon dioxide expands and extends said alimentary canal of said subject.

22. A method useful according to claim 21, wherein said potassium carbonate is present in an amount of 0.2 to 13% by weight.

23. A method useful according to claim 22, wherein said potassium carbonate is present in an amount of 0.3 to 3% by weight.

24. A method useful according to claim 23, wherein said potassium carbonate is present in an amount of 0.4 to 1% by weight.

* * * * *

EXCLUSIVITY SUMMARY for NDA # 20-292 SUPPL # —

Trade Name FerriSeltz **Generic Name** ferric ammonium citrate, brown
Applicant Name Oncomembrane **HFD-**160

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # see attached pages; no active NDA's with this active moiety
NDA # (all previously approved have been discontinued or
NDA # withdrawn) _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /[redacted]/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /[redacted]/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 07B

Investigation #2, Study # 04A

Investigation #3, Study # —

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ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

APPEARS THIS WAY
ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 07B

Investigation #2, Study # 04A

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND YES /X/ NO /___/ Explain: _____

Investigation #2

IND YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / X /

If yes, explain: _____

_____

_____

_____

Kim Colangelo 9-30-97
Signature Date
Title: Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

10/14/97
Signature of Division Director Date

cc: Original NDA 20-292
HFD-160/Division File
HFD-85/Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-292 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-160 Trade and generic names/dosage form: [illegible] ([illegible] for oral administration) Action: AP AE NA

Applicant [illegible], Inc. Therapeutic Class 3S

Indication(s) previously approved —

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication in this application [illegible] (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

X c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- X (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[illegible signature], CSO 9-15-97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-292
HFD-160/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/15/97)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

CORRESPONDENCE

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 15, 1997

FROM: Kim Colangelo, Consumer Safety Officer KMC 9-15-97

SUBJECT: Phase 4

TO: NDA 20-292

cc: Orig. NDA 20-292
HFD-160/Division File

APPEARS THIS WAY
ON ORIGINAL

ONCOMEMBRANE, INC.®
Innovation for Global Health

NEW CORRESPONDENCE

1201 Third Ave Suite 3300 Seattle WA 98101 Phone 206 622-6626 Fax 206 622-2259

November 20, 1996

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Rockville, MD 20857

REVIEWS COMPLETED
DSO ACTION:
LETTER N.A.I.
DATE

Re: NDA 20-292
FerriSeltz™ (ferric ammonium citrate, brown)
Response to FDA action letter dated November 15, 1996

Dear Dr. Love:

We acknowledge receipt of your letter of November 15, 1996, which indicated that the NDA for FerriSeltz is approvable pending the resolution of certain issues. Under 21 CFR 314.110(a)(1), we hereby notify FDA of our intention to file an amendment to provide the information requested in the November 15, 1996 letter. We understand that the notice of intent to file an amendment constitutes an agreement by Oncomembrane to extend the review period for 45 days after the date FDA receives the amendment, to permit the agency to review the amendment.

We also acknowledge requirements to

- Submit three copies of the introductory promotional material that we propose to use for FerriSeltz;
- Provide updated safety information, including results of trials that were still ongoing at the time of the NDA submission and an analysis of digestive system adverse events by time after ingestion and by volume of FerriSeltz ingested; and

We will submit the additional information required on CMC issues, the safety update, and introductory promotional materials as separate amendments to NDA 20-292 and the Phase 4 study information as an amendment to

Sincerely,

Toshihiko Tanaka
CEO & President

ONCOMEMBRANE,INC.®
Innovation for Global Health

1201 Third Ave., Suite 5300, Seattle, WA 98101 Phone: (206) 622-6626 Fax: (206) 622-2259

ORIG AMENDMENT

ORIGINAL
bc

October 17, 1996

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

FOOD & DRUG ADMINISTRATION
Attention: Ms. Susan Cusack
Office of Drug Evaluation I
Division of Medical Imaging, Surgical
and Dental Drug Products (HFD-160)
Parklawn Building, Room 18B-09
5600 Fishers Lane
Rockville, MD 20857

RE: FerriSeltz™(ferric ammonium citrate, brown)
NDA #20-292
Amendment: Disbarment Statement

Dear Madam/Sir:

Oncomembrane certifies that it did not and will not use in any capacity the services of any person debarred under subsections "a" or "b" (Section 306 "a" or "b") in connection with this application.

Sincerely,

Toshihiko Tanaka
President

TT/bc

FILE IN THIS WAY
ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 18 1996
HFD-160

MEMORANDUM OF TELECON

DATE: September 9, 1997

APPLICATION NUMBER: NDA 20-292; FerriSeltz

BETWEEN:

Name: J. Kay Noel, Ph.D.
Phone: 510-525-4250
Representing: J. Kay Noel & Associates (consultant for Oncomembrane, Inc.)

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Information Request

I phoned Dr. Noel to request an electronic copy of the submitted draft labeling, and of p. 1-37 of the Safety Update dated February 20, 1997. Dr. Noel agreed to submit these items.

Kim Colangelo
Consumer Safety Officer

cc: Original NDA 20-292
HFD-160/Div. File
HFD-160/Kim Colangelo/Paserchia

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 3, 1997

APPLICATION NUMBER: NDA 20-292; FerriSeltz

BETWEEN:

Name: J. Kay Noel, Ph.D.
Phone: 510-525-4250
Representing: J. Kay Noel & Associates (consultant for Oncomembrane, Inc.)

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: PDUFA Goal Date and Environmental Assessment (EA) Issues

I phoned Dr. Noel to verify the PDUFA goal date for this application, since an acknowledgment letter with this information was not sent to the Sponosr. The PDUFA goal date is October 14, 1997. Dr. Noel was aware of the date.

I informed Dr. Noel that the review of the submitted EA was complete, and deficiencies had been noted. Dr. Noel stated that she was aware of the new regulations concerning EA requirements, and the option of requesting a categorical exclusion. I informed Dr. Noel that I would be sending the EA deficiencies via facsimile. Once she and Oncomembrane, Inc., had an opportunity to review them, I requested that she notify me whether they would be addressing the deficiencies or requesting categorical exclusion. Dr. Noel agreed.

APPEARS THIS WAY
ON ORIGINAL

Kim Colangelo
Kim Colangelo
Consumer Safety Officer

cc: Original NDA 20-292
HFD-160/Div. File
HFD-160/Kim Colangelo
HFD-160/Salazar

APPEARS THIS WAY
ON ORIGINAL

TELECON

NDA 20-292

JUL 23 1997

Oncomembrane, Inc.
c/o Otsuka America, Inc.
One Embarcadero Center, Suite 2020
San Francisco, CA 94111

Attention: Kay Noel, Ph.D.

Dear Dr. Noel:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for FerriSeltz® (ferric ammonium citrate, brown).

We also refer to your letter of June 27, 1997, notifying us that the corporate address has been changed from Oncomembrane, Inc., 1201 Third Avenue, Suite 5300, Seattle, WA, 98101 to Oncomembrane, Inc., c/o Otsuka America, Inc., One Embarcadero Center, Suite 2020, San Francisco, CA, 94111.

Our records have been revised to reflect this change.

If you have any questions, please contact Ms. Christy Wilson at (301) 443-3500.

Sincerely yours,

7/21/97

James Cheever, D.M.D.
Associate Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-292
HFD-160/Div Files
HFD-92/DDM-DIAB
HFD-160/CSO/SCusack
HFD-160/Chow
HFD-160/Salazar
HFD-160/Sadrieh
DISTRICT OFFICE

Drafted by: CWilson/July 21, 1997/n20292.coa
F/T by: CWilson/July 21, 1997

CHANGE OF ADDRESS

APPEARS THIS WAY
ON ORIGINAL