CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-961/S-009

Trade Name: Ganite

Generic Name: (gallium nitrate)

Sponsor: Genta Inc.

Approval Date: September 17, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-961/S-009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-961/S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-961/S-009

Genta Inc.
Attention: Paul Manley
Vice President, Regulatory Affairs
Two Connell Drive
Berkeley Heights, NJ 07922

Dear Mr. Manley:

Please refer to your supplemental new drug application dated April 16, 2003, received April 17, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ganite (gallium nitrate injection).

We acknowledge receipt of your submissions dated August 27, and September 10 and 12, 2003.

This supplemental new drug application proposes an updated package insert, vial label, and carton label.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed-upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert dated September 12, 2003, and vial label and carton label dated September 10, 2003). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 19-961/S-009." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
9/17/03 04:04:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-961/S-009

LABELING

Proposed Labeling Changes

Current Labeling

APPROVED

SEP 17 2003

Ganite™

(gallium nitrate injection)

WARNING

Concurrent use of gallium nitrate with other potentially nephrotoxic drugs (e.g., aminoglycosides, amphotericin B) may increase the risk for developing severe renal insufficiency in patients with cancer-related hypercalcemia. If use of a potentially nephrotoxic drug is indicated during gallium nitrate therapy, gallium nitrate administration should be discontinued and it is recommended that hydration be continued for several days after administration of the potentially nephrotoxic drug. Serum creatinine and urine output should be closely monitored during and subsequent to this period. Ganite therapy should be discontinued if the serum creatinine level exceeds 2.5 mg/dL.

DESCRIPTION

Gallium nitrate injection is a clear, colorless, odorless, sterile solution of gallium nitrate, a hydrated nitrate salt of the group IIIa element, gallium. Gallium nitrate is formed by the reaction of elemental gallium with nitric acid, followed by crystallization of the drug from the solution. The stable, nonahydrate, $Ga(NO_3)_3 \cdot 9H_2O$ is a white, slightly hygroscopic, crystalline powder of molecular weight 417.87, that is readily soluble in water. Each mL of Ganite (gallium nitrate injection) contains gallium nitrate 25 mg (on an anhydrous basis) and sodium citrate dihydrate 28.75 mg. The solution may contain sodium hydroxide or hydrochloric acid for pH adjustment to 6.0-7.0.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ganite exerts a hypocalcemic effect by inhibiting calcium resorption from bone, possibly by reducing increased bone turnover. Although *in vitro* and animal studies have been performed to investigate the mechanism of action of gallium nitrate, the precise mechanism for inhibiting calcium resorption has not been determined. No cytotoxic effects were observed on bone cells in drug-treated animals.

Proposed Labeling Changes

Current Labeling

Pharmacokinetics

Gallium nitrate was infused at a daily dose of 200 mg/m^2 for 5 (n=2) or 7 (n=10) consecutive days to 12 cancer patients. In most patients apparent steady-state is achieved by 24 to 48 hours. The range of average steady-state plasma levels of gallium observed among 7 fully evaluable patients was between 1134 and 2399 ng/mL. The average plasma clearance of gallium (n=7) following daily infusion of gallium nitrate at a dose of 200 mg/m^2 for 5 or 7 days was 0.15 L/hr/kg (range: 0.12 to 0.20 L/hr/kg). In one patient who received daily infusion doses of 100, 150 and 200 mg/m^2 the apparent steady-state levels of gallium did not increase proportionally with an increase in dose. Gallium nitrate is not metabolized either by the liver or the kidney and appears to be significantly excreted via the kidney. Urinary excretion data for a dose of 200 mg/m^2 has not been determined.

Cancer-Related Hypercalcemia

Hypercalcemia is a common problem in hospitalized patients with malignancy. It may affect 10-20% of patients with cancer. Different types of malignancy seem to vary in their propensity to cause hypercalcemia. A higher incidence of hypercalcemia has been observed in patients with non-small cell lung cancer, breast cancer, multiple myeloma, kidney cancer, and cancer of head and neck. Hypercalcemia of malignancy seems to result from an imbalance between the net resorption of bone and urinary excretion of calcium. Patients with extensive osteolytic bone metastases frequently develop hypercalcemia: this type of hypercalcemia is common with primary breast cancer. Some of these patients have been reported to have increased renal tubular calcium resorption. Breast cancer cells have been reported to produce several potential bone-resorbing factors which stimulate the local osteoclast activity. Humoral hypercalcemia is common with the solid tumors of the lung, head and neck, kidney, and ovaries. Systemic factors (e.g., PTH-rP) produced either by the tumor or host cells have been implicated for the altered calcium fluxes between the extracellular fluid, the kidney, and the skeleton. About 30% of patients with myeloma develop hypercalcemia associated with extensive osteolytic lesions and impaired glomerular filtration. Myeloma cells have been reported to produce local factors that stimulate adjacent osteoclasts.

Proposed Labeling Changes	Current Labeling
	Hypercalcemia may produce a spectrum of signs and symptoms including: anorexia, lethargy, fatigue, nausea, vomiting, constipation, dehydration, renal insufficiency, impaired mental status, coma and cardiac arrest. A rapid rise in serum calcium may cause more severe symptoms for a given level of hypercalcemia. Since calcium is bound to serum proteins, which may fluctuate in concentration as a response to changes in blood volume, changes in total serum calcium (especially during rehydration) may not accurately reflect changes in the concentration of free-ionized calcium. In the absence of a direct measurement of free-ionized calcium, measurement of the serum albumin concentration and correction of the total serum calcium concentration may help in assessing the severity of hypercalcemia. The patient's acid-base status should also be taken into consideration while assessing the degree of hypercalcemia. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without diuretics). The patient's cardiovascular status should be taken into consideration in the use of saline. In patients who have an underlying cancer type that may be sensitive to corticosteroids (e.g., hematologic cancers), the use or addition of corticosteroid therapy may be indicated. ***Hypocalcemic Activity*** A randomized double-blind clinical study comparing Ganite with calcitonin was conducted in patients with a serum calcium concentration (corrected for albumin)$\geq$ 12.0 mg/dL following 2 days of hydration. Ganite was given as a continuous intravenous infusion at a dose of 200 mg/m^2/day for 5 days and calcitonin was given intramuscularly at a dose of 8 I.U./kg every 6 hours for 5 days. Elevated serum calcium (corrected for albumin) was normalized in 75% (18 of 24) of the patients receiving Ganite and in 27% (7 of 26) of the patients receiving calcitonin (p=0.0016). The time-course of effect on serum calcium (corrected for albumin) is summarized in the following table.

Proposed Labeling Changes

Current Labeling

Change in Corrected Serum Calcium by Time From Initiation of Treatment

Time Period[1]	Mean Change in Serum Calcium (mg/dL)[2]	
(hours)	GANITE	Calcitonin
24	–0.4	–1.6*
48	–0.9	–1.4
72	–1.5	–1.1
96	–2.9*	–1.1
120	–3.3*	–1.3

[1]Time after initiation of therapy in hours.
[2]Change from baseline in serum calcium (corrected for albumin).
*Comparison between treatment groups ($p<0.01$).

The median duration of normocalcemia/hypo - calcemia was 7.5 days for patients treated with Ganite and 1 day for patients treated with calcitonin. A total of 92% of patients treated with Ganite had a decrease in serum calcium (corrected for albumin) $\geq$ 2.0 mg/dL as compared to 54% of the patients treated with calcitonin ($p=0.004$).

An open-label, non-randomized study was conducted to examine a range of doses and dosing schedules of Ganite for control of cancer-related hypercalcemia. The principal dosing regimens were 100 and 200 mg/m^2/day, administered as continuous intravenous infusions for 5 days. Ganite, at a dose of 200 mg/m^2/day for 5 days was found to normalize elevated serum calcium levels (corrected for albumin) in 83% of patients as compared to 50% of patients receiving a dose of 100 mg/m^2/day for 5 days. A decrease in serum calcium (corrected for albumin) $\geq$ 2.0 mg/dL was observed in 83% and 94% of patients treated with Ganite at dosages of 100 and 200 mg/m^2/day for 5 days, respectively. There were no significant differences in the proportion of patients responding to Ganite when considering either the presence or absence of bone metastasis, or whether the tumor histology was epidermoid or nonepidermoid.

INDICATIONS AND USAGE

Ganite is indicated for the treatment of clearly symptomatic cancer-related hypercalcemia that has not responded to adequate hydration. In general, patients with a serum calcium (corrected for albumin) < 12 mg/dL would not be expected to be symptomatic.

Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without diuretics). In the treatment of cancer-related hypercalcemia, it is important first to establish adequate hydration, preferably with intravenous saline, in order to increase the renal excretion of calcium and correct dehydration caused by hypercalcemia.

CONTRAINDICATIONS

Ganite should not be administered to patients with severe renal impairment (serum creatinine > 2.5 mg/dL).

WARNINGS

(See boxed **WARNING**.) The hypercalcemic state in cancer patients is commonly associated with impaired renal function. Abnormalities in renal function (elevated BUN and/or serum creatinine) have been observed in clinical trials with Ganite. **It is strongly recommended that serum creatinine be monitored during Ganite therapy.** Since patients with cancer-related hypercalcemia are frequently dehydrated, it is important that such patients be adequately hydrated with oral and/or intravenous fluids (preferably saline) and that a satisfactory urine output (a urine output of 2 L/day is recommended) be established before therapy with Ganite is started. Adequate hydration should be maintained throughout the treatment period, with careful attention to avoid overhydration in patients with compromised cardiovascular status. Diuretic therapy should not be employed prior to correction of hypovolemia. Ganite therapy should be discontinued if the serum creatinine level exceeds 2.5 mg/dL.

The use of Ganite in patients with marked renal insufficiency (serum creatinine > 2.5 mg/dL) has not been systematically examined. If therapy is undertaken in patients with moderately impaired renal function (serum creatinine 2.0 to 2.5 mg/dL), frequent monitoring of the patient's renal status is recommended. Treatment should be discontinued if the serum creatinine level exceeds 2.5 mg/dL.

Combined use of Ganite with other potentially nephrotoxic drugs (e.g., aminoglycosides, amphotericin B) may increase the risk of developing renal insufficiency in patients with cancer-related hypercalcemia (see boxed **WARNING**).

Proposed Labeling Changes

A symptom complex of dyspnea (associated with interstitial pneumonitis in some instances), mouth soreness, and asthenia has been reported in a small number of multiple myeloma patients receiving low dose (40 mg) gallium nitrate subcutaneously in addition to oral cyclophosphamide and prednisone. The serious nature of the underlying condition of these patients precludes a precise understanding of the relationship of these events to either gallium nitrate treatment alone or with cyclophosphamide.

Current Labeling

PRECAUTIONS

General

Asymptomatic or mild to moderate hypocalcemia (6.5–8.0 mg/dL, corrected for serum albumin) occurred in approximately 38% of patients treated with Ganite in the controlled clinical trial. One patient exhibited a positive Chvostek's sign. If hypocalcemia occurs, Ganite therapy should be stopped and short-term calcium therapy may be necessary.

Laboratory Tests Renal function (serum creatinine and BUN) and serum calcium must be closely monitored during Ganite therapy. In addition to baseline assessment, the suggested frequency of calcium and phosphorus determinations is daily and twice weekly, respectively. Ganite should be discontinued if the serum creatinine exceeds 2.5 mg/dL.

Drug Interactions The concomitant use of highly nephrotoxic drugs in combination with Ganite may increase the risk for development of renal insufficiency (see **WARNINGS**).

Available information does not indicate any adverse interaction with diuretics such as furosemide.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential of gallium nitrate. Gallium nitrate is not mutagenic in standard tests (i.e., Ames test and chromosomal aberration studies on human lymphocytes).

Usage in Pregnancy *Pregnancy Category C.* Animal reproduction studies have not been conducted with gallium nitrate. It is also not known whether gallium nitrate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Ganite should be administered to a pregnant woman only if clearly needed.

Nursing Mothers It is not known whether gallium nitrate is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from gallium nitrate, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use The safety and effectiveness of Ganite in children have not been established.

ADVERSE REACTIONS

Kidney

Adverse renal effects, as demonstrated by rising BUN and creatinine, have been reported in about 12.5% of patients treated with Ganite. In a controlled clinical trial of patients with cancer-related hypercalcemia, two patients receiving Ganite and one patient receiving calcitonin developed acute renal failure. Due to the serious nature of the patients' underlying conditions, the relationship of these events to the drug was unclear. Ganite should not be administered to patients with serum creatinine >2.5 mg/dL (see **CONTRAINDICATIONS** and **WARNINGS**).

Metabolic

Hypocalcemia may occur after Ganite treatment (see **PRECAUTIONS**).

Transient hypophosphatemia of mild-to-moderate degree may occur in up to 79% of hypercalcemic patients following treatment with Ganite. In a controlled clinical trial, 33% of patients had at least 1 serum phosphorus measurement between 1.5-2.4 mg/dL, while 46% of patients had at least 1 serum phosphorus value <1.5 mg/dL. Patients who develop hypophosphatemia may require oral phosphorus therapy.

Decreased serum bicarbonate, possibly secondary to mild respiratory alkalosis was reported in 40–50% of cancer patients treated with Ganite. The cause for this effect is not clear. This effect has been asymptomatic and has not required specific treatment.

Hematologic

The use of very high doses of gallium nitrate (up to 1400 mg/m^2) in treating patients for advanced cancer has been associated with anemia, and several patients have received red blood cell transfusions. Due to the serious nature of the underlying illness, it is uncertain that the anemia was caused by gallium nitrate.

Blood Pressure

A decrease in mean systolic and diastolic blood pressure was observed several days after treatment with gallium nitrate in a controlled clinical trial. The decrease in blood

pressure was asymptomatic and did not require specific treatment.

Visual and Auditory

In cancer chemotherapy trials, a small proportion (<1%) of patients treated with multiple high doses of gallium nitrate combined with other investigational anticancer drugs, have developed acute optic neuritis. While these patients were critically ill and had received multiple drugs, a reaction to high-dose gallium nitrate is possible. Most patients had full recovery; however, at least one case of permanent blindness has been reported. One patient with cancer-related hypercalcemia was reported to develop decreased hearing following gallium nitrate administration. Due to the patient's underlying condition and concurrent therapies, the relationship of this event to gallium nitrate administration is unclear. Tinnitus and partial loss of auditory acuity have been reported rarely (<1%) in patients who received high-dose gallium nitrate as anticancer treatment.

Miscellaneous

Other clinical events reported in association with gallium nitrate treatment for cancer as well as cancer-related hypercalcemia include: nausea and/or vomiting, tachycardia, lethargy, confusion, ~~~~~ dreams and hallucinations, diarrhea, constipation, lower extremity edema, hypothermia, fever, dyspnea, rales and rhonchi, anemia, leukopenia, paresthesia, skin rash, pleural effusion, and pulmonary infiltrates. Due to the serious nature of the underlying condition of these patients, the relationship of these events to therapy with gallium nitrate is unknown.

A single case of encephalopathy followed rapidly by coma and death has been reported after treatment in a cancer chemotherapy trial with gallium nitrate 300 mg/m^2/day for 7 days. Treatment with gallium nitrate other than as described in this labeling may be complicated by adverse events not listed.

OVERDOSAGE

Rapid intravenous infusion of gallium nitrate or use of doses higher than recommended (200 mg/m^2) may cause nausea and vomiting and a substantially increased risk of renal insufficiency. In the event of overdosage, further drug administration should be discontinued, serum calcium should be monitored, and the patient should receive vigorous intravenous hydration, with or without diuretics, for 2-3 days. During this time period, renal function and urinary output should be carefully monitored so that fluid intake and output are balanced.

Proposed Labeling Changes

48 hours at room temperature (15°C to 30°C)

Current Labeling

DOSAGE AND ADMINISTRATION

The usual recommended dose of Ganite is 200 mg per square meter of body surface area (200 mg/m^2) daily for 5 consecutive days. In patients with mild hypercalcemia and few symptoms, a lower dosage of 100 mg/m^2/day for 5 days may be considered. If serum calcium levels are lowered into the normal range in less than 5 days, treatment may be discontinued early. The daily dose must be administered as an intravenous infusion over 24 hours. The daily dose should be diluted, preferably in 1,000 mL of 0.9% Sodium Chloride Injection USP, or 5% Dextrose Injection USP, for administration as an intravenous infusion over 24 hours. Adequate hydration must be maintained throughout the treatment period, with careful attention to avoid overhydration in patients with compromised cardiovascular status. Controlled studies have not been undertaken to evaluate the safety and effectiveness of retreatment with gallium nitrate.

When Ganite is added to either 0.9% Sodium Chloride Injection USP or 5% Dextrose Injection USP, it is stable for [redacted] or for 7 days if stored under refrigeration (2°C to 8°C). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Ganite™ (gallium nitrate injection) is supplied as a 5-unit carton, NDC 66657-301-05.

Each carton contains 5 single-dose, flip-top vials (NDC 66657-301-01) each containing 500 mg of gallium nitrate (25 mg/mL) in 20 mL.

Store at controlled room temperature 20°-25°C (68°-77°F).

Contains no preservative. Discard unused portion.

Rx only

Proposed Labeling Changes	Current Labeling
	Ganite™ is a trademark of Genta Incorporated. Manufactured for: Genta Incorporated Berkeley Heights, NJ 07922 1-888-GO-GENTA Revised: ~~April~~ September 2003 30105901

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-961/S-009

CHEMISTRY REVIEW(S)

From: Hedin, Durand M
Sent: Thursday, September 04, 2003 9:28 AM
To: 'Manley@genta.com'
Subject: Labeling Comments for NDA 19-961/009

Dear Mr. Manley:

We have the following labeling comments from the chemistry review of NDA 19-961/S-009.

1. On the immediate container (vial) label, the statement "Dilute in an isotonic saline or dextrose solution"

2. In the package insert, DOSAGE AND ADMINISTRATION section the sentence

   s

   statement from the SoloPak label "When Ganite is added to either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, it is stable for 48 hours at room temperature (15°C to 30°C) for 7 days if stored under refrigeration (2°C to 8°C)."

If you have any question please contact me.

Sincerely,

Randy Hedin

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/s/

Randy Hedin
9/4/03 09:39:04 AM
CSO

	1.ORGANIZATION	2. NDA NUMBER
CHEMIST'S REVIEW	DMEDP, HFD-510	**19-961**
3. NAME AND ADDRESS OF APPLICANT		4.SUPPLEMENT NUMBER,DATE
Genta Incorporated Two Connell Drive Berkeley Heights, New Jersey 07922		**SLR-009** (PA), dated 4-16-03 User Fee Date: 10-17-03
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	
Ganite™	Gallium nitrate injection	8.AMENDMENTS/REPORT,DATE
7. SUPPLEMENT PROVIDES FOR:		
New labeling for the drug product (package insert, vial label, and carton label)		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11.RELATED IND/NDA/DMF
Small volume parenteral (LVP)	Rx only	NDA 19-961/S-007 NDA 19-961/S-008
12. DOSAGE FORM	13. POTENCY	
Sterile solution for injection	25 mg/mL (500 mg/vial)	

14. CHEMICAL NAME AND STRUCTURE.

- Name: *Gallium nitrate hydrate*
- Empirical formula: $Ga(NO_3)_3 \cdot 9H_2O$ (nonahydrate)
- Molecular weight: 255.74 g/mol (anhydrous basis)
- CAS Registry Number [69365-72-6]

15. COMMENTS

NDA 19-961/SLR-009 is a prior-approval supplement providing labeling for the drug product, as manufactured for Genta Incorporated.

sNDA's 19-961/S-007 (drug substance issues) and 19-961/S-008 (drug product CMC issues) were previously approved. NDA 19-961/SLR-009 provides a revised package insert, vial label, and carton label, indicating the new NDC number and new distributor. This review addresses the portions of the labeling which are related to CMC issues (DESCRIPTION SECTION, HOW SUPPLIED SECTION, DOSAGE AND ADMINISTRATION, nomenclature, statement of manufacturer, and storage statement). The statement "Rx only" was added per the requirements of FDAMA and the storage statement was revised to reflect the actual stability storage conditions used to support the expiry. The instructions in the DOSAGE AND ADMINISTRATION section were based on an admixture study provided in sNDA 19-961/S-008 (and reproduced in this sNDA as Attachment 2). This study was reviewed by the microbiology staff for sterility assurance,

16. CONCLUSION AND RECOMMENDATION

The labeling provided for Ganite™ (gallium nitrate injection) is not adequate for the drug product. See draft letter of deficiencies to be communicated to the NDA holder.

17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
David B. Lewis, Ph.D.		August 13th, 2003

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

3 Page(s) Withheld

1 § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry- 19-961
5009

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/s/

David Lewis
9/3/03 01:51:20 PM
CHEMIST
Not adequate. Deficiency letter prepared.
I corrected the typo on p. 4.

Mamta Gautam-Basak
9/3/03 01:57:02 PM
CHEMIST
Concur, comments to be forwarded to the applicant.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-961/S-009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-961/S-009

Genta Inc.
Attention: Paul Manley
Vice President, Regulatory Affairs
Two Connell Drive
Berkeley Heights, NJ 07922

Dear Mr. Manley:

We acknowledge receipt of your October 21, 2003, submission containing final printed labeling in response to our September 17, 2003 letter approving your supplemental new drug application for Ganite (gallium nitrate injection).

We have reviewed the labeling (package insert, vial label, and carton label) that you submitted in accordance with our September 17, 2003 letter, and we find them acceptable.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
5/12/04 02:22:41 PM

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 19-961/S-009

Name of Drug: Ganite (gallium nitrate injection)

Sponsor: Genta Inc.

Material Reviewed

Submission Dates:

- October 21, 2003, submission containing final printed labeling (FPL) of the package insert, and carton and vial labels.

Background and Summary Description:

Ganite was studied under three INDs, IND [redacted] IND [redacted] and IND [redacted] Ganite was approved for marketing on January 21, 1991, for the indication, "treatment of clearly symptomatic cancer-related hypercalcemia that has not responded to adequate hydration." [redacted] labeling was approved on September 17, 2003.

Review

Vial

The submitted FPL of the vial label (Identifier Number 30101402, No Revised Date) submitted October 21, 2003 was compared to the draft labeling submitted September 10, 2003 and approved on September 17, 2003.

The label is identical.

Carton

The submitted FPL of the carton label (Identifier Number 30105501, No Revised Date) submitted October 21, 2003 was compared to the draft labeling submitted September 10, 2003 and approved on September 17, 2003.

The label is identical.

Package Insert

The submitted FPL of the package insert (Identifier Number 30105901, Revised Date, September 2003) submitted October 21, 2003 was compared to the draft labeling submitted September 12, 2003 and approved on September 17, 2003.

The label is identical except for the telephone number in the "Manufactured for:" section. The telephone number in the draft label is 1-888-GO-GENTA, and the number in the FPL is 1-888-TO-GENTA.

Conclusions

The labels are acceptable. Issue an Acknowledge and Retain letter.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

{See appended electronic signature page}

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/s/

Randy Hedin
5/12/04 02:04:13 PM
CSO

From: Hedin, Durand M
Sent: Friday, September 12, 2003 12:30 PM
To: 'Ganeshan, Shanthi'
Subject: NDA 19-961/S-009 Ganite (gallium nitrate) Injection

Dear Ms. Ganeshan,

The following is what we recommended in our October 29, 1998 letter to SoloPak. The proposed additions to the label, as originally submitted by SoloPak, are shown in italicized font, and the Division's requested changes are double underlines. This is how the Division wants the sentences to read.

If you have any questions please contact me.

Sincerely,

Randy Hedin

Precautions

Drug Interactions

.....Available information does not indicate any adverse interaction with diuretics such as furosamide. *A symptom complex of dyspnea (associated with interstitial pneumonitis in some instances), mouth soreness, and asthenia has been reported in a small number of multiple myeloma patients receiving low dose (40 mg) gallium nitrate subcutaneously in addition to oral cyclophosphamide and prednisone. The serious nature of the underlying condition of these patients precludes a precise understanding of the relationship of these events to either gallium nitrate treatment alone or with cyclophosphamide.*

Adverse Reactions

Miscellaneous

.....pleural effusion, and pulmonary infiltrates. *A single case of encephalopathy followed rapidly by coma and death has been reported after treatment in a cancer chemotherapy trial with gallium nitrate 300 mg/m2/day for 7 days. Treatment with gallium nitrate other than as described in this labeling may be complicated by adverse events not listed.*

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/s/

Randy Hedin
9/12/03 03:20:09 PM
CSO

Division of Metabolic and Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: 19-961/S-009

Name of Drug: Ganite (gallium nitrate injection)

Sponsor: Genta Inc.

Material Reviewed

Submission Dates:

- April 16, 2003, submission containing draft labeling of the package insert, and carton and vial labels.

Background and Summary Description:

Ganite was studied under three INDs, [redacted] Ganite was approved for marketing on January 21, 1991, for the indication, "treatment of clearly symptomatic cancer-related hypercalcemia that has not responded to adequate hydration." [redacted]

Review

Vial

The submitted draft vial label (Identifier Number 30101401, No Revised Date) submitted April 16, 2003 was compared to the Final Printed labeling (FPL) for the approved product vial label (Identifier Number 401362/G-90, No Revised Date) acknowledged and retained May 22, 1992.

Genta has reformatted the vial label with multiple changes. The changes are acceptable.

Carton

The submitted draft carton (Identifier Number 30105501, No Revised Date) submitted April 16, 2003 was compared to the FPL for the approved product carton (Identifier Number 551-20, No Revised Date) acknowledged and retained May 22, 1992.

Genta has reformatted the carton with multiple changes. The changes are acceptable.

Package Insert

The submitted draft package insert (PI) dated April 16, 2003 (Identifier Number 30105901, Revised April 2003), was compared to the final printed label PI submitted October 11, 1994 (Identifier Number 45524C, Revised February 1994) for Supplement 004. This CBE was approved on March 27, 1995.

The changes we requested are as follows:

1. In the Drug Interactions subsection of the PRECAUTIONS section . . ." to "A symptom complex of dyspnea (associated with interstitial pheumonitis in some instances), mouth soreness, and asthenia . . ."

2. In the Miscellaneous subsection of the ADVERSE REACTIONS section please change the sentence that begins "A single case . . ." to "A single case of encephalopathy followed rapidly by coma and death has been reported . . ."

The sentence that reads, should read "A symptom complex of dyspnea (associated with interstitial pheumonitis in some instances), mouth soreness, and asthenia has been reported in a small number of multiple myeloma patients receiving low dose (40mg) gallium nitrate subcutaneously in addition to oral cyclophosphamide and prednisone. The serious nature of the underlying condition of these patients precludes a precise understanding of the

relationship of these events to either gallium nitrate treatment alone or with cyclophosphamide."

ADVERSE REACTIONS "A single case of encephalopathy followed rapidly by coma and death has been reported after treatment in a cancer chemotherapy trial with gallium nitrate 300 mg/m^2/day for 7 days. Treatment with gallium nitrate other than as described in this labeling may be complicated by adverse events not listed."

In the **DOSAGE AND ADMINISTRATION** section the space between "over" and "hydration"

The second to last sentence of the **DOSAGE AND ADMINISTRATION** section has been changed from, , "When Ganite is added to either 0.9% Sodium chloride injection U.S.P. or 5% Dextrose Injection USP it is stable for

The **HOW SUPPLIED** section is changed as follows:

- 'Ganite (gallium nitrate injection) is supplied as a 5-unit carton, NDC 66657-301-05."
- "Each carton contains 5 single-dose, flip-top vials (NDC 66657-301-01) each containing 500 mg of gallium nitrate (25 mg/mL) in 20 mL."
- The phrase, "Store at controlled room temperature 20°-25°C (68°-77°F)."
- "**Rx only**." This is in response to the February 1, 2002 Federal Register notice. See Guidance for Industry, Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements. This is an acceptable change.

- The phrase. ~~"Ganite is a trademark of Genta Incorporated. Manufactured for: Genta Incorporated Berkeley Heights, NJ 07922 Toll free number."~~

Conclusions

The vial and carton labels, and the change to Rx only are acceptable. The medical officer and chemistry reviewer should make a determination if the changes listed above are acceptable from their point of view.

Reviewed by: Randy Hedin, R.Ph., Senior Regulatory Management Officer

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/s/

Randy Hedin
8/18/03 09:09:27 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-961/S-009

PRIOR APPROVAL SUPPLEMENT

Genta Incorporated
Attn: Paul F. Manley
Vice President, Regulatory Affairs
Two Connell Drive
Berkeley Heights, NJ 07922

Dear Mr. Manley:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: GANITE™ (gallium nitrate injection)

NDA Number: 19-961

Supplement number: S-009

Date of supplement: April 16, 2003

Date of receipt: April 17, 2003

This supplemental application proposes a package insert, vial label, and carton label.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 16, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 17, 2003.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic & Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
4/24/03 03:13:32 PM