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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-305

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-305 (N000-AZ) (Response to a deficiency Letter)

PRODUCT: Sodium Iodide I-131 solution (1000 mCi/mL) for oral administration using hard gelatin capsules intended for further compounding by the radiopharmacist, either as oral solution or solution in capsule form prior to administration to the patient.

INDICATION: Treatment of various thyroid diseases including hyperthyroidism, Grave's disease, thyrotoxicosis, papillary and follicular carcinoma of the thyroid.

DOSE: Varies according to extent of disease, stage of disease and diagnostic uptake.

REVIEWER: Christy S. John, Ph.D.

TEAM LEADER: Young Moon Choi, Ph.D.

SUBMISSION DATE: July 31, 2002

ASSIGNED DATE: August 14, 2002

SPONSOR: DRAXIMAGE, Inc.
16751 Trans-Canada Highway, Kirkland, Quebec, Canada

A. SYNOPSIS

On 8/24/2002, the sponsor, Draximage, Inc. submitted a new drug application (NDA #21305) for sodium Iodide I-131 Solution USP. The sponsor requested approval of the proposed product, ^{131}I NaI, at a radioactive concentration of 37 gigabecquerels/ml (1000 mCi/mL). This product is intended for further compounding by the radiopharmacist, either as an oral solution or in capsule form prior to administration to the patient. The sponsor did not seek new or different indication.

The Agency reviewed this NDA and found the information submitted to be inadequate. A deficiency letter was issued on June 29, 2001 to the sponsor. Most of the deficiencies related to chemistry, manufacturing and control issues. The clinical pharmacology section of the letter reported the following two deficiencies:

1. "Lack of sufficient data to support a waiver of in-vivo bioequivalence and bioavailability for the solution. In addition to the lack of finished dosage form information, for the solution, the DraxImage product does not contain the exact same inactive ingredients as any of the reference listed drugs as required under 21 CFR 320.22. The closest (but not identical in both active and inactive ingredients)

Reference Listed Drug (RLD) solutions are manufactured by Bracco as Iodotope. This prevents the conclusion that the proportions of the inactive ingredients are the same and that the bioequivalence and bioavailability would be the same as RLD.

2. Lack sufficient data to support a waiver of in-vivo bioequivalence and bioavailability data from the derived final dosage form (capsule). In addition to the lack of data stated in section I.C above, based on the RLD information, there are apt to be substantial quantitative and qualitative differences in the ingredients of the marketed capsules and a capsule prepared from the high concentration."

In the present submission, the sponsor provided the rationale of biowaiver with comparative disintegration data on gelatin capsules. This review describes the background information and focussed on the rationale of the biowaiver.

B. BACKGROUND

Radioisotope of iodine (I-131) has been routinely available for clinical application since 1940s. Sodium iodide (I-131) has been used as a diagnostic agent and a therapeutic for a wide variety of thyroid disorders for the last 40 years. For a diagnostic use the preferred agent of choice is sodium iodide (I-123) but I-131 is predominantly used for therapeutic applications. The dose of I-131 administered to patients depends on the extent and type of disease and can range from a few mCi to few hundred mCi.

The rationale for developing a high concentration 1 Ci/mL Sodium Iodide Solution (HCNA I-131) is to afford the convenience of a low volume patient dosing for high activity therapy doses. This allows preparation of high activity single capsule patient therapy doses instead of multiple capsules by using lower concentration solutions, as currently available. The proposed higher strength allows the radiopharmaceutical to deliver the necessary therapeutic dose to patients with metastatic thyroid cancer in a concentrated dose. This would consist of a few milliliters of oral solution or one or two capsules instead of four to eight capsules that are often required to deliver the desired therapeutic dose.

The sponsor requested that the Agency waive the requirement for the submission of evidence demonstrating in vivo bioequivalence for Sodium Iodide I-131 Solution USP, Therapeutic Oral. The sponsor claims that their product meets the provisions of 21 CFR 320.22(b)(3)(i) and (iii).

It is well known in the literature that orally administered I-131 is rapidly absorbed from the gastrointestinal tract and can be detected in the thyroid gland within a few minutes of oral administration. Iodide ion is also taken up by the salivary glands, gastric mucosa, choroid plexus and nasal pharynx. In euthyroid subjects with normal renal function approximately 50-75% of the carrier free orally administered iodide is excreted in urine within 48 hrs. A small amount is also excreted via the colon and sweat glands. Within thyroid gland the iodide is rapidly oxidized and bound organically. Following oral

administration approximately 40% of the activity has an effective half-life of 0.3 days and 60% has an effective half-life of 7.61 days. The different half-lives represent the excretion rates from the inorganic and organic iodine pools, respectively.

There are three approved NDAs for ^{131}I-sodium iodide capsules. The following table is taken from the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluation" 20th Edition, 2000.

Sponsor	Product Name	Strengths	NDA Number	Solution Description
Bracco	Iodotope	1 – 130 mCi	N10929 001	0.85% potassium phosphate dibasic (buffer), 0.01% edetate disodium (stabilizer), NaOH or HCl (pH adjustment 7.5-9.0)
Bracco	Iodotope	1-150 mCi	N10929 003	
CIS	Sodium Iodide I-131	100 mCi	N17316 002	4.2 mg/mL phosphate buffer
Mallinckrodt	Sodium Iodide I-131	15-100 mCi	N16517 002	Phosphate dibasic (500 mg/capsule)
		0.8-100 mCi	N16517 001	

The following table lists the comparison of the inactive ingredients of DraxImage and Bracco products:

Component	Composition (per vial solution)		Composition (per capsule solution)	
	DraxImage	Bracco	DraxImage	Bracco
NaI	250 and 500 mCi	7, 14, 28, 70 or 106 mCi	Upto 150 mCi	Upto 150 mCi
Disodium Phosphate Anhyd, USP	<40 mg		mg	mg max
$Na_2S_2O_3.5H_2O$	<4.4 mg		mg	ng max
Disodium edetate dihydrate, USP (stabilizer)	<2.0 mg	1.0 mg	mg	
Dibasic sodium phosphate (matrix)	N/A	N/A	300 mg	N/A
(matrix)	N/A	N/A	N/A	mg

There are very minor differences in the chemical compositions in capsule presentation of NaI-131 manufactured by DraxImage and Bracco. Bracco used as a matrix whereas DraxImage is proposing to use dibasic sodium phosphate as a matrix for its manufacture.

According to a letter by DraxImage submitted to FDA in response to IR letter of December 14, 2000, the sponsor stated that they believe that a waiver for the in-vivo bioequivalency is justified for the following reasons:

1. The Sodium Iodide I-131 used in the preparation of the DraxImage product is from the same primary manufacturer as all the other approved products containing Sodium iodide I-131, namely
2. The capsule preparation method proposed by the sponsor in the Package Insert is in fact identical to the currently approved Sodium Iodide I-131 capsule product (NDA 016517) from Mallinckrodt Medical in that they both use powdered anhydrous Disodium Phosphate USP as inorganic substrate in a gelatin capsule.
3. Since the active drug substance is the same and the substrate is the same then the key issue for an in vitro bioequivalency study would be to compare dissolution of capsules prepared by the methods proposed by DraxImage in the Package Insert and to approved reference standards. There are two approved reference standards:

   Mallinckrodt Medical NDA 015517 Sodium Iodide I-131 Capsules
   Bracco Diagnostics NDA 01929 Sodium Iodide I-131 Capsules

4. The Active Drug Substance, Sodium Iodide, is a simple inorganic salt and is fully dissociated in solution into iodide anions and sodium cations. The substrate disodium phosphate is also fully dissociated in solution into phosphate anions and sodium cations. Thus once dissolved the capsule contents form a true solution and as such issues like bioavailability and bioequivalence are no longer applicable. The only limiting factor is the rate of capsule dissolution.

   In order to make such a comparison as realistic as possible DraxImage arranged for a US radiopharmacy to undertake the comparison. Their report follows:

   The following is the data collected from a USP-DI disintegration time test of Mallinckrodt and Bracco NaI-131 therapy capsules versus our compounded NaI-131 product. The test was conducted using a USP disintegration apparatus and a 0.1N HCl solution heated to 37 °C.

Capsule	Initial Rupture (min)	Soft Mass (min)
Bracco	1.15	2:00
Mallinckrodt	0:59	3:00
Radiopharmacy(1)	0:52	3:00 (Inner capsule rupture at 2:00)
Radiopharmacy(2)	1:10	3:40 (Inner capsule rupture at 3:00)

   In conclusion, the results of the testing prove there is no distinguishable difference between the disintegration rates of all three capsules.

C. Reviewer's Comments:
   According to 21 CFR 320.22 an applicant can be granted a bioequivalence or bioavailability waiver provided "The drug product contains an active drug ingredient in the same concentration and dosage form as drug product that is the subject of an approved full new drug application; and contains no inactive gradient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety".

   This reviewer is of the opinion that once the capsules disintegrates in stomach, disodium phosphate will completely dissociate instantaneously. Therefore, the bioavailability/bioequivalence concerns do not apply. This is further strengthened by the experimental evidence that the disintegration rate in vitro (in 1.1 N HCl) for DraxImage capsules is almost the same as Mallinckrodt and Bracco capsules. Also, this reviewer is of the opinion that there are no known chemical interactions between disodium phosphate and iodide ions. Furthermore, there is no known effect of phosphate ions or polyethylene glycol on iodide ion absorption in-vivo.

   The sponsor has submitted additional data for the disintegration of Sodium Iodide I-131 Solution in single and doubly encapsulated gelatin capsules. The results showed that the doubly encapsulated capsules show a slightly longer lag time until total activity is

released. This lag time varies from approximately 5 minutes to approximately 15 minutes. Total disintegration was always obtained within 30 minutes. The minor changes in the inactive ingredients are not likely to have any significant effect on the bioavailability of I-131.

In conclusion, the DraxImage product does not contain the exact same inactive ingredients as other approved drug. However, based upon the known solubility and dissociation of inactive ingredients as well as the rapid in-vivo absorption of iodide ion, this reviewer is of the opinion that these changes in inactive ingredients do not significantly affect the in-vivo absorption of iodide ion. Therefore, the bioequivalence/bioavailablility waver is granted to the sponsor.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, has reviewed the sponsor's response to the deficiency letter issued by the Agency and found that this submission is acceptable from pharmacokinetics perspective.

/S/

Christy S. John, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence

/S/

Young Moon Choi, Ph.D.
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/s/

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BIOPHARMACEUTICS