CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-586

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA#	21-586 (N-000)
PRODUCT	DuraPrep™ Surgical Solution
FORMULATION	Iodophor (0.7% available iodine) and isopropyl alcohol (74% w/w)
SUBMISSION DATE	10/24/03, 3/9/04, and 4/20/04
SUBMISSION TYPE	Original New Drug Application
SPONSOR	3M Health Care, St. Paul, MN 55144-1000
OCPB DIVISION	Division of Pharmaceutical Evaluation III
MEDICAL DIVISION	Division of Anti-Infective Drug Products
REVIEWER	Charles R. Bonapace, Pharm.D.
TEAM LEADER	Venkat R. Jarugula, Ph.D.

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

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I. EXECUTIVE SUMMARY

DuraPrep Surgical Solution (iodophor [0.7% available iodine] and isopropyl alcohol, 74% w/w) is a patient preoperative skin preparation that has been marketed in the US as an over-the-counter (OTC) product since 1988. 3M Health Care submitted an original New Drug Application (NDA) for DuraPrep surgical solution to establish antimicrobial effectiveness of the combination product since the test methods specified in the Tentative Final Monograph (TFM) are generally applicable to water-soluble formulations and do not directly apply to DuraPrep solution (since it dries to a water-insoluble film). An approved NDA for DuraPrep surgical solution will be required for the product to remain on the OTC market when the TFM is finalized. Modification of the TFM methods were found acceptable by the Agency for the pivotal clinical studies to assess the efficacy and safety of DuraPrep solution in addition to demonstrating the contribution of iodine in DuraPrep solution.

The sponsor assessed the potential for iodine absorption by comparing a single application of DuraPrep solution to Betadine solution and three days of iodine-rich meals in 12 subjects (Study LIMS 1621). Since DuraPrep is an OTC product that has been marketed for more than a decade, the Agency and sponsor came to an agreement during a teleconference on January 17, 2003 that submission of the results from the absorption study would be used for informational purposes only and the decision to approve the product would not be based on the results from this study.

The analytical method of Study LIMS 1621 utilized acid bromination with colorimetric determination to determine total plasma and urine iodine concentrations following application of DuraPrep solution and Betadine solution. Although the analytical method is supposedly validated, the sponsor was unable to provide analytical validation data (i.e., accuracy, precision, specificity, and stability) when requested by the reviewer to support the method used to determine the concentration of iodine in plasma and urine. Thus, the reviewer recommends that the information obtained from this study be used with caution when comparing the absorption of iodine from DuraPrep solution, Betadine solution, and iodine-enriched meals and not for making regulatory decisions.

A. RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III (OCPB/DPE-III) has reviewed NDA 21-586 and it is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. Although the analytical method used to determine plasma and urine iodine concentrations in Study LIMS 162 was supposedly validated, the sponsor was unable to provide data to support the validation of the assay. Thus, the reviewer recommends that data obtained from Study LIMS 1621 should be used for informational purposes only. No additional studies are recommended to assess the absorption of iodine from topical administration of DuraPrep solution.

B. PHASE IV COMMITMENTS:

No Phase IV commitments are recommended.

C. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The sponsor was unable to provide any analytical validation data for Study LIMS 1621 when requested by the reviewer. Assuming that the analytical method used to determine plasma and urine iodine concentrations was previously validated, the reviewer reported the observations of Study LIMS1621 for informational purposes. In this study, the sponsor assessed the absorption of a single application of DuraPrep surgical solution compared to Betadine solution and following three days of iodine-rich meals. In study LIMS 1621, 11.6 mL of DuraPrep (equivalent to 0.08 g of iodine) or 8 mL of Betadine (equivalent to 0.08 g of iodine) was applied to the backs of healthy volunteers. The formulation of DuraPrep used in study LIMS 1621 was different than the marketed US formulation and consisted of iodophor (0.69% available iodine) and isopropyl alcohol 70% w/w compared to the US formulation

which consists of iodophor (0.7% available iodine) and isopropyl alcohol 74% w/w. Blood samples for iodine concentration determination were obtained for 28 hrs after application and urine samples were obtained for 72 hrs. The mean plasma concentration-time profiles of iodine (not corrected for baseline) were initially greater in subjects who received DuraPrep solution compared to Betadine solution, whereas the mean plasma concentration-time profiles were similar in subjects who received DuraPrep solution and three days of iodine-rich meals. The mean AUC_{0-28} for DuraPrep was slightly greater (6.0%) than the mean AUC_{0-28} for Betadine and similar to the mean AUC_{0-28} following three days of iodine-rich meals. Upon correction of iodine plasma concentrations for baseline values, mean plasma iodine concentrations were similar to or below baseline values after a single dose application of DuraPrep or Betadine and three days of iodine-rich meals. The mean amount of iodine excreted in urine during the 0-24 hr and 24-48 hr periods was greater for DuraPrep (224 µg and 228 µg, respectively) compared to Betadine (122 µg and 128 µg, respectively) and after three days of iodine-rich meals (177 µg and 114 µg, respectively). The sponsor also assessed the clinical impact of a single application of DuraPrep solution, Betadine solution, and three days of iodine-rich meals on thyroid function on days 1, 3, and 8. The mean T3, T4, and TSH concentrations were not significantly different between the DuraPrep solution, Betadine solution, and three days of iodine-rich meals when compared on the same day (day 1, 3, or 8). Although the mean plasma iodine AUC_{0-28} and urinary excretion of iodine were greater following a single application of DuraPrep compared to Betadine, the increased plasma concentrations do not appear to be clinically relevant compared to iodine-rich meals based on thyroid function.

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RD/FT Initialed by Venkat R. Jarugula, Ph.D.,_____
Team Leader

cc:
Division File: NDA 21-586
HFD-520 (CSO/Dillon-Parker)
HFD-520 (MO/Mulinde, Bostwick)
HFD-880 (Division File, Lazor, Selen, Jarugula, Bonapace)
CDR (Clin. Pharm./Biopharm.)

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II. QUESTION-BASED REVIEW

A. General Attributes

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

DuraPrep surgical solution was introduced into the US market in 1988 as an over-the-counter (OTC) drug product under the 1978 Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products. In 1994, a second TFM was published that was more specific in its allowable active ingredient description (povidone-iodine rather than iodophor). The sponsor met with the Agency in December 1994 to discuss the chemistry of DuraPrep solution and the implications of the 1994 TFM, at which time the Agency indicated that the DuraPrep solution chemistry was not covered under the scope of the TFM. The Agency further determined that DuraPrep solution would be allowed to stay on the market while 3M worked toward the submission of a New Drug Application (NDA). During a Pre-IND meeting in October 1995, it was determined that a NDA would be submitted for DuraPrep solution for the indication of patient pre operative skin preparation. Because DuraPrep solution contains 2 active ingredients, iodophor and isopropyl alcohol, the Agency considers the product a combination product. As such, the contribution of each active ingredient would need to be demonstrated. Further, the Agency stated that human absorption data would not be required for NDA approval since DuraPrep is an OTC product that has been on the market for more than a decade; however, the FDA requested that 3M submit the final study report of a French absorption study (LIMS 1621) as part of the NDA.

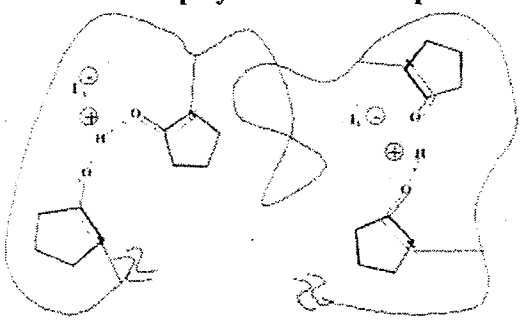
The sponsor was requested to submit the complete analytical validation data for Study LIMS 1621 (e.g., accuracy, precision, specificity, and stability). In a submission dated 4/20/04, the sponsor responded that they do not have any analytical validation data relative to accuracy, precision, specificity, and stability. Thus, the findings of the absorption study (Study LIMS 1621) in this review are for information purposes assuming that the analytical method was previously validated.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

DuraPrep surgical solution is a topical antiseptic product consisting of 2 active ingredients, an iodophor (0.7% available iodine) and isopropyl alcohol (74% w/w). The iodophor active ingredient, iodine acrylate copolymer solution, contains a

Figure 1. Chemical structure of DuraPrep copolymer (left) and copolymer-iodine complex (right)

Copolymer **Copolymer-iodine complex**



The composition of DuraPrep solution is shown in Table 1. [redacted] ratio based on weight.

Table 1. Composition of DuraPrep surgical solution

Ingredient	Amount (%w/w)	Function
Iodine, USP	0.7%	Active
Isopropyl Alcohol	74.0%	Active/Vehicle
[redacted]		

3. What is the proposed mechanism of action and therapeutic indications?

DuraPrep contains iodine acrylate copolymer and isopropyl alcohol as active ingredients. The iodine acrylate copolymer remains dissolved in isopropyl alcohol/water until applied dermally. As the isopropyl alcohol evaporates, the copolymer forms a water insoluble film that is intended to have a sustained antiseptic effect. The antiseptic activity of DuraPrep surgical solution is due to the liberation of iodine. The microbicidal effects of iodine are the result of cell wall penetration, oxidation, and substitution of microbial contents with free iodine. There are no chemical reactions taking place on the skin, only the evaporation of the volatile compounds (alcohol and water) that deposits the copolymer film containing iodine onto the surface of the skin. DuraPrep surgical solution is intended for use as a patient preoperative skin preparation.

4. What are the proposed dosage and route of administration?

DuraPrep surgical solution contains 0.7% available iodine as a copolymer/iodine complex and isopropyl alcohol 74% w/w. It is intended for use as a topical agent only. The actual dose will vary according to the area of skin that requires disinfection. The sponsor proposes marketing DuraPrep solution in sealed glass ampules containing either 6 mL or 26 mL of active drug substance. Each unit is housed in a [redacted] plastic applicator, with a [redacted] sponge at the end through which the solution is dispensed for topical application to a patient's skin prior to surgery.

B. General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor submitted the results from a single clinical pharmacology study (Study LIMS 1621) that assessed the absorption of iodine from DuraPrep surgical solution (iodophor [0.69% available iodine]) and Betadine solution (povidone iodine, 1%). This study was a Phase 1, single-blind, comparative, randomized, cross-over study in twelve healthy subjects. A supplementary non-randomized sequence (period 3) was performed to compare plasma and urine iodine concentrations, thyroid hormone plasma concentrations (T3 and T4), and TSH plasma concentrations after consumption of three days of iodine-rich meals to a single application of DuraPrep or Betadine on intact skin.

The sponsor performed two pivotal Phase 3 clinical studies to demonstrate the effectiveness of DuraPrep solution against resident skin flora on the abdomen and groin (LIMS 8304 and LIMS 8918). In Study LIMS 8304, both DuraPrep solution and Hibiclens cleanser (chlorhexidine gluconate) met the TFM reduction criteria of a 2-log reduction on the abdomen and a 3-log reduction on the groin. In LIMS 8918, while DuraPrep solution and Hibiclens cleanser met the 2-log reduction on the abdomen, neither product met the 3-log reduction on the groin, although both products performed equally. Study LIMS 8918 also evaluated the durability and persistence of the antimicrobial activity of DuraPrep film (DuraPrep solution once it is dry) and Betadine cleanser and solution (Betadine once it is dry) following a wash with autologous blood and saline.

The contribution of iodine to the antimicrobial efficacy of the formulation was demonstrated by the enhanced reduction of a bacterial challenge using DuraPrep solution compared with DuraPrep w/o I_2 in studies LIMS 8197 and LIMS 9302.

2. Are the active moieties in plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

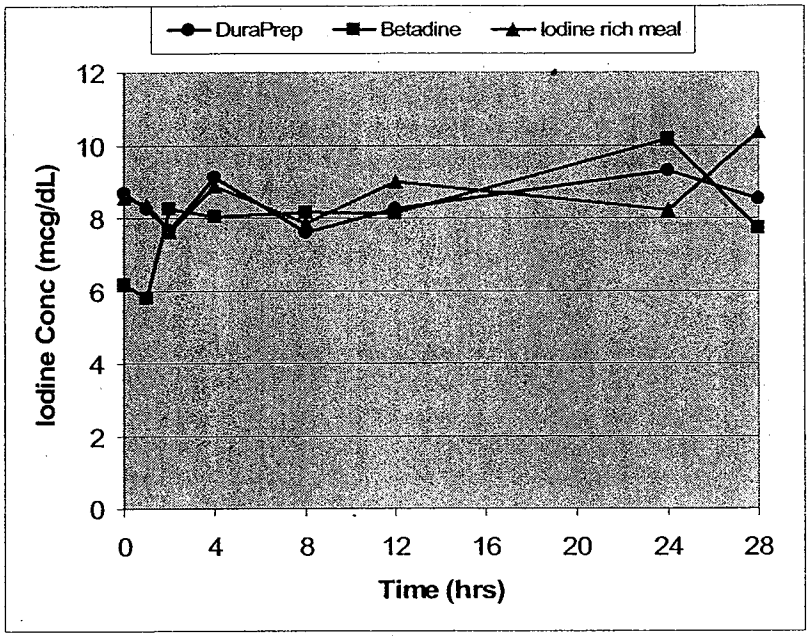
The concentrations of iodine (expressed as I^-) in plasma and urine samples were not appropriately measured for regulatory purposes. The sponsor used an acid bromination and colorimetric determination method to determine plasma and urine concentration of iodine. Assuming that the analytical method was previously validated, the reviewer reported the observations of Study LIMS 1621 in this review. However, the sponsor was unable to provide analytical validation data upon request to support the accuracy, precision and specificity of the analytical method. Thus, the results from this study should be used for informational purposes and should not be used to make regulatory decisions (See II.F, Analytical Section).

3. What are the PK characteristics of the drug and its major metabolite?

The sponsor performed a single Phase 1 cross-over study in healthy subjects to assess the absorption of iodine from DuraPrep surgical solution compared to Betadine aqueous solution. A non-randomized third period was performed to assess the impact of three days of iodine-rich meals on plasma and urine iodine concentrations.

The mean plasma concentration-time profiles of iodine (not corrected for baseline) following a single application of DuraPrep and Betadine or following a high iodine meal are shown in Figure 2. The mean plasma concentrations of iodine from DuraPrep were initially greater-than those from Betadine and similar to those following iodine-rich alimentation.

Figure 2. Mean iodine plasma concentration-time profiles (not corrected for baseline) following a single application of DuraPrep and Betadine or three days of iodine-rich meals



The mean (SD) pharmacokinetic parameter estimates for iodine (not corrected for baseline) after a single application of DuraPrep or Betadine and following the consumption of iodine-rich meals are shown in Table 2. The mean C_{max} following application of DuraPrep was 17.9% greater than the mean C_{max} after application of Betadine. The mean AUC_{0-28} for DuraPrep was 6.0% greater than the mean AUC_{0-28} for Betadine. When compared to plasma concentrations of iodine following three days of iodine-rich meals, the mean plasma iodine C_{max} values for DuraPrep and Betadine were 11.8% and 25.2% lower, respectively. The mean AUC_{0-28} for DuraPrep was similar to the mean value after three days of iodine-rich meals. However, the mean AUC_{0-28} for Betadine was 5.9% lower than the mean value after three days of iodine-rich meals. Thus, the differences between the mean C_{max} and AUC_{0-28} values among three groups were less than 25%.

NOTE: The lower mean iodine C_{max} and AUC_{0-28} values in the Betadine group compared to DuraPrep and three days of iodine-rich meals may be due to the lower mean iodine baseline values for subjects in the Betadine group.

Table 2. Mean (CV%) pharmacokinetic parameter estimates for iodine (not corrected for baseline) following a single application of DuraPrep or Betadine and three days of iodine-rich meals

Parameter	DuraPrep	Betadine	Iodine-rich meals
C_{max} (µg/dL)	12.6 (28%)	10.6 (29%)	14.2 (16%)
T_{max} (hrs)	6.6 (131%)	16.2 (63%)	13.5 (85%)
AUC_{0-28} (µg*hr/dL)	231 (36%)	219 (46%)	232 (17%)

C. Intrinsic factors

Not applicable.

D. Extrinsic factors

1. Drug-drug interactions

Since DuraPrep solution is applied topically and the plasma concentrations of iodine are similar following the application of DuraPrep and several days of iodine-rich meals, the sponsor did not perform any studies to investigate the pharmacological effects when DuraPrep surgical solution is used concomitantly with other medications. No studies were conducted regarding interaction with other topically applied materials.

E. General Biopharmaceutics

1. What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The formulation of DuraPrep surgical solution used in the pivotal Phase 3 clinical efficacy studies (LIMS 8304 and LIMS 8918) is the same as the currently marketed formulation available over-the-counter. Thus, the sponsor has not performed any bioequivalence studies comparing the formulation used in the Phase 3 clinical trials to the currently marketed formulation.

F. ANALYTICAL SECTION

1. How are the active moieties identified and measured in plasma in the clinical pharmacology and biopharmaceutics studies?

The active components of DuraPrep surgical solution consist of iodophor and isopropyl alcohol. Iodine is absorbed systemically following release from iodophor and its concentration in plasma and urine was determined using acid bromination with colorimetric determination and UV spectrophotometer at ———— Although the analytical method was supposedly validated, the sponsor was unable to provide analytical validation data when requested by the reviewer to support the method used to determine the concentration of iodine in plasma and urine. Thus, the results obtained from this analytical method are presented for informational purposes only.

2. Which metabolites have been selected for analysis and why?

Isopropyl alcohol and water constitute the vehicle for the iodophor. Following the evaporation of isopropyl alcohol, the iodophor is deposited on the surface of the skin in a water-impermeable layer. Since iodine is absorbed systemically, the sponsor determined the concentration of iodine in plasma and urine for analysis. There are no metabolites of iodine.

3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The concentrations of total iodine are reported. Since study LIMS 1621 compared the concentrations of iodine in plasma and urine after administration of DuraPrep surgical solution and Betadine aqueous solution in the same subjects, the use of total iodine concentrations is appropriate.

4. What bioanalytical methods are used to assess concentrations?

See IV.F.1 stated above.

4.a What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curve for iodine in plasma and urine ranged from —µg/dL to— µg/dL. The concentration of iodine in several plasma and urine samples exceeded the supposedly validated concentration range (— µg/dL to—µg/dL) following the application of DuraPrep solution, Betadine solution, and iodine-rich meals. The sponsor did not provide any evidence that plasma or urine samples were further diluted such that the resulting concentration would be within the validated range.

4.b What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower and upper limits of quantification (LLOQ) were —µg/dL and—µg/dL, respectively based on a 1 mL aliquot of plasma or urine.

4.c What is the accuracy, precision, and selectivity at these limits?

The sponsor did not report the accuracy and precision of iodine in plasma and urine at these limits.

4.d What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The stability of iodine in standard stock solution (—µg/mL), in plasma and urine samples at ambient temperature, and after several freeze-thaw cycles was not reported. However, based on the properties of iodine in solution, it would not be anticipated that iodine is unstable in water, plasma, or urine.

4.e What is the QC sample plan?

The sponsor's quality control sample plan was not stated.

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III. LABELING RECOMMENDATIONS

The sponsor's proposed label is shown in Section IV. Appendix A - Proposed Label. The reviewer has no labeling recommendations.

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

IV. APPENDIX C - INDIVIDUAL STUDY REPORTS

Study of transdermal absorption of two iodine solutions: DuraPrep surgical solution (alcohol solution) versus Betadine (aqueous solution), after single cutaneous application in twelve normal healthy volunteers (Study LIMS 1621)

Date: June 28, 1989 to October 19, 1989
Clinical Site: [redacted]

OBJECTIVES:
The objectives of this study were to 1) compare the transdermal absorption of iodine from two antiseptic solutions after single cutaneous application for 24 hrs; 2) to evaluate the influence of both preparations on thyroid function (T3, T4) and TSH after single cutaneous applications of two iodine solutions for 24 hrs; 3) to assess iodemia and ioduria after single cutaneous application of two iodine solution for 24 hrs; and 4) to asses the impact of iodemia, ioduria, and thyroid hormone plasma concentrations (T3 and T4) and TSH plasma concentrations after three days of iodine-rich alimentation.

FORMULATIONS:
DuraPrep surgical solution (iodophor [0.69% available iodine], isopropyl alcohol 70% w/w)
Betadine solution (povidone iodine, 1%)

STUDY DESIGN:
This study was a Phase 1, single-blind, comparative, randomized, cross-over study in twelve healthy subjects (20 to 30 yrs of age) consisting of a one-week running period, followed by the two sequences of treatment with a two-week washout period between each sequence and a one-week follow-up period. A supplementary non-randomized sequence (period 3) was performed to assess iodemia, ioduria, thyroid hormone plasma concentrations (T3 and T4), and TSH plasma concentrations after consumption of three days of iodine-rich meals (alginates and caragenates) for lunch and dinner on day -2, day -1, and day 1.

The two iodine-containing surgical solutions consisted of DuraPrep surgical solution (available iodine 0.69%) and Betadine solution (povidone iodine, 1%). Subjects received 11.6 mL of DuraPrep surgical solution and 8 mL of Betadine solution (corresponding to 0.08 mg of iodine) applied on the back of each subject. Each solution was spread for 5 min using a brush within a 25 cm × 36 cm rectangle (900 cm^2). The treated surface was not washed for 24 hrs. After 24 hrs, the treated surface was washed using alcohol for DuraPrep and water for Betadine.

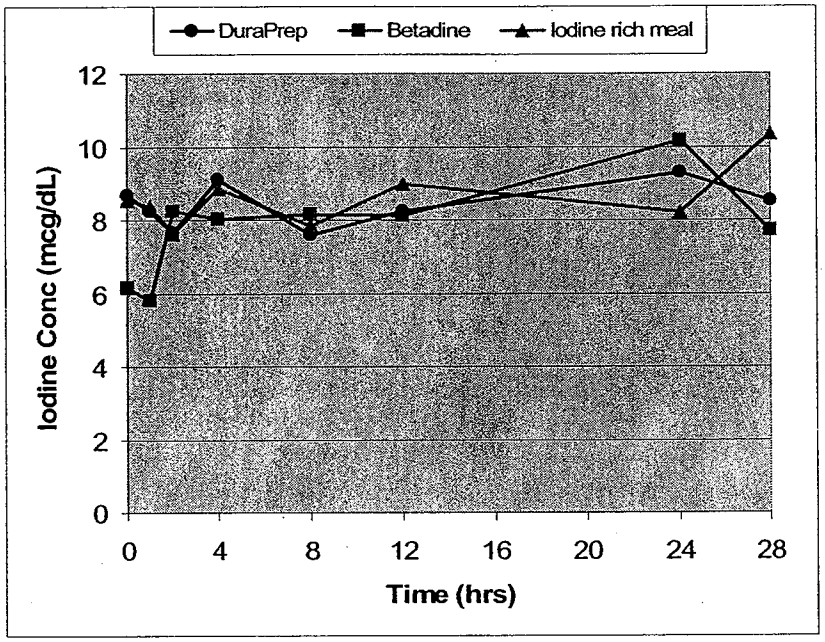
Food and fluid intake were controlled during the two days preceding the administration and during the day following application. Meals were poor in iodine and identical for the two days preceding the administration and during the day following the application with both two randomized sequences.

Blood samples were obtained following application of each treatment prior to drug application (0 hrs) and at 1, 2, 4, 8, 12, 24, and 28 hrs after each application. Blood samples were obtained for T3, T4, and TSH determination on day 1 (prior to application) and again on day 3 and day 8 following each application.

Urine was collected for 24 hrs prior to application and during the following intervals following each application: -24 to 0, 0-4, 4-8, 8-12, 12-24, 24-48, and 48-72 hrs.

the DuraPrep group were initially greater-than subjects in the Betadine group and similar to subjects receiving iodine-rich alimentation.

Figure 3. Mean iodine plasma concentration-time profiles (not corrected for baseline) following a single application of DuraPrep or Betadine and three days of iodine-rich meals



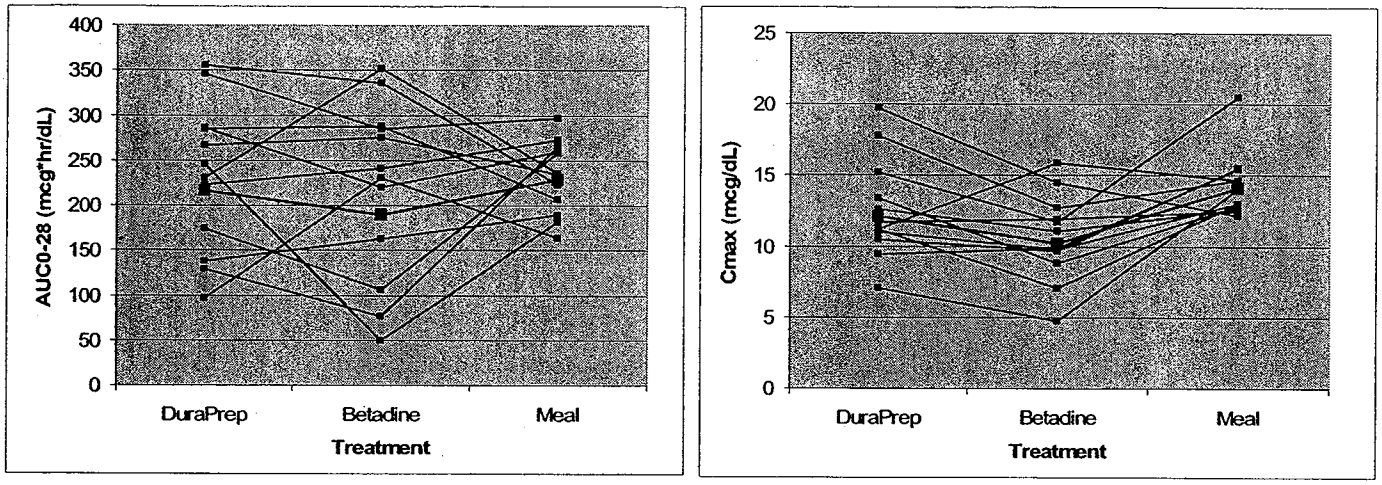
The mean (CV%) pharmacokinetic parameter estimates for iodine (based on concentrations not corrected for baseline) after a single application of DuraPrep or Betadine and following consumption of iodine-rich meals are shown in Table 3. The mean C_{max} following application of DuraPrep was 17.9% greater than the mean C_{max} after application of Betadine. The mean AUC_{0-28} for DuraPrep was 6.0% greater than the mean AUC_{0-28} for Betadine. When compared to plasma concentrations of iodine following three days of iodine-rich meals, the mean plasma iodine C_{max} values for DuraPrep and Betadine were 11.8% and 25.2% lower, respectively. The mean AUC_{0-28} for DuraPrep was similar to the mean value after three days of iodine-rich meals. However, the mean AUC_{0-28} for Betadine was 5.9% lower than the mean value after three days of iodine-rich meals.

Table 3. Mean (CV%) pharmacokinetic parameter estimates for iodine following a single application of DuraPrep or Betadine and three days of iodine-rich meals

Parameter	DuraPrep	Betadine	Iodine-rich meals
C_{max} (µg/dL)	12.6 (28%)	10.6 (29%)	14.2 (16%)
T_{max} (hrs)	6.6 (131%)	16.2 (63%)	13.5 (85%)
AUC_{0-28} (µg*hr/dL)	231 (36%)	219 (46%)	232 (17%)

The individual AUC_{0-28} and C_{max} values and geometric mean following the application of a single dose of DuraPrep or Betadine and three days of iodine-rich meals are shown in the stick plots of Figure 4. There was a greater degree of variability following the application of Betadine compared to DuraPrep for AUC_{0-28} (CV 46% compared to 36%) but not C_{max}. The geometric mean AUC_{0-28} and C_{max} values following three days of iodine-rich meals were greater than following a single dose application of DuraPrep or Betadine.

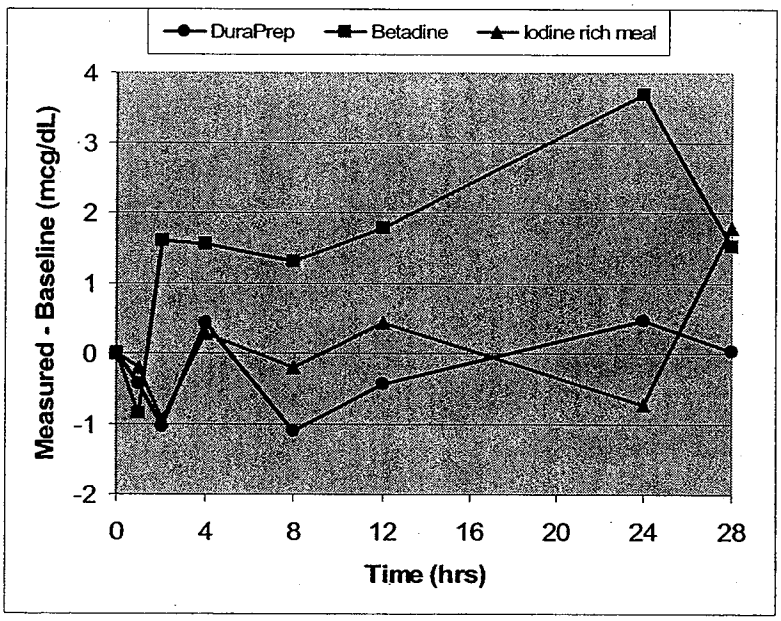
Figure 4. Individual iodine $AUC_{0-\infty}$ and C_{max} values following a single application of DuraPrep or Betadine and three days of iodine-rich meals (geometric mean demonstrated by the bold red line)



NOTE: The bold red line represents the geometric mean values

The mean iodine plasma concentrations corrected for baseline are shown in Figure 5. In general, the mean iodine concentrations corrected for baseline (measured concentration - baseline concentration) remained close to zero for DuraPrep and iodine-rich meals. The mean iodine concentrations corrected for baseline did not exceed 0.47 µg/dL, 3.69 µg/dL, and 1.79 µg/dL for DuraPrep, Betadine, and three days of iodine-rich meals, respectively.

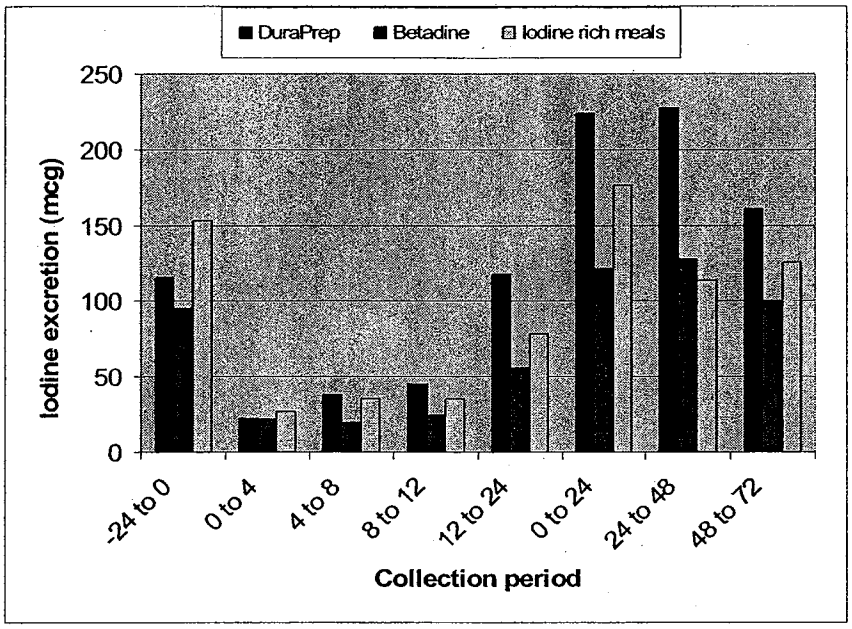
Figure 5. Mean iodine plasma concentration-time profiles corrected for baseline (measured - baseline) following a single application of DuraPrep or Betadine and three days of iodine-rich meals



The mean amount of iodine excreted in the urine for up to 72 hrs following a single application of DuraPrep or Betadine and after three days of iodine-rich meals is shown in Figure 6. When compared to baseline (-24 to 0 hrs), an additional 118 µg and 27 µg of iodine were excreted from 0 to 24 hrs after a

single application of DuraPrep and Betadine, respectively. The mean amount of iodine excreted during the 0 to 24 hr and 24 to 48 hr periods was greater for DuraPrep (224 µg and 228 µg, respectively) compared to Betadine (122 µg and 128 µg, respectively). The mean amount of iodine excreted over 24 hrs after three days of iodine-rich meals (177 µg) following was significantly lower than a single application of DuraPrep and significantly greater than a single application of Betadine.

Figure 6. Mean iodine content excreted in urine (µg/period) following a single application of DuraPrep or Betadine and three days of iodine-rich meals



NOTE: The 0 to 24 hr interval represents the cumulative excretion of iodine between 0 and 24 hrs

Table 2. Mean (CV%) T3, T4, and TSH plasma concentrations in samples collected after a single application of DuraPrep or Betadine and three days of iodine-rich meals

Parameter	Day	DuraPrep	Betadine	Iodine-rich meals
T3 (ng/mL)	Day 1	1.77 (21%)	1.88 (22%)	1.78 (21%)
	Day 3	1.75 (24%)	1.78 (18%)	1.88 (15%)
	Day 8	1.83 (20%)	1.89 (16%)	1.92 (19%)
T4 (ng/mL)	Day 1	82 (25%)	78 (24%)	78 (18%)
	Day 3	73 (25%)	74 (21%)	79 (17%)
	Day 8	76 (25%)	76 (22%)	78 (26%)
TSH (ng/mL)	Day 1	1.95 (47%)	1.88 (55%)	2.04 (51%)
	Day 3	2.74 (55%)	2.41 (38%)	2.39 (53%)
	Day 8	2.47 (38%)	2.77 (50%)	2.24 (51%)

Following a single application of either DuraPrep or Betadine, the mean T3, T4, and TSH concentrations were not significantly different on days 1, 3, or 8 within each treatment arm (comparing different days) except for T3 plasma concentrations after application of Betadine from day 3 (1.78 ng/mL) to day 8 (1.89 ng/mL), T4 plasma concentrations after application of DuraPrep from day 1 (82 ng/mL) to day 3 (73 ng/mL), and TSH plasma concentrations after application of Betadine from day 1 (1.88 ng/mL) to day 3 (2.77 ng/mL). There were no significant differences between the mean T3, T4, and TSH concentrations

on the same day (days 1, 3, or 8) following a single application of DuraPrep or Betadine and consumption of iodine-rich meals.

CONCLUSIONS:
Assuming the analytical method was previously validated, the following conclusions can be drawn:

1. The mean iodine plasma AUC_{0-28} based on concentrations not corrected for baseline were similar following a single topical application of Betadine and DuraPrep using an equal amount of iodine (0.08 mg).

2. Upon correction of iodine plasma concentrations for baseline values, mean plasma iodine concentrations after a single dose application of DuraPrep were similar to or below mean iodine concentrations following administration of Betadine or three days of iodine-rich meals.

3. The amount of iodine excreted in the urine from the 0 to 24 hrs was greatest following a single application of DuraPrep (224 µg) followed by Betadine (122 µg) and three days of iodine-rich meals (177 µg).

4. The increased excretion of iodine following a single administration of DuraPrep solution compared to Betadine solution is probably not clinically significant based on similar T3, T4, and TSH plasma concentrations between the two treatments and three days of iodine-rich meals.

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