CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-097

ADMINISTRATIVE DOCUMENTS

Patent Information-Paragraph I Certification

In accordance with Title 21 of the Code of Federal Regulations, Part 314, Section 50, paragraph (i) [21 CFR 314.50(i)] and Part 314, Section 53, paragraph (c) [21 CFR 314.53(c)], InKine Pharmaceutical Company, Inc (InKine) is submitting the following information for the patent described in this application. InKine certifies that this patent information has not been previously submitted to the U.S. Food and Drug Administration.

(1) General requirements

(i) Patent number and the date on which the patent will expire

Patent Number: *5,616,346*
Date of Patent: *April 01, 1997*
Date of Expiration: *April 01, 2017*

(ii) Type of patent

Patent number 5,616,346 is a method of use patent.

(iii) Name of the patent owner

Craig A. Aronchick, M.D.
903 Bryn Mawr Avenue
Penn Valley, PA 19072

(iv) Not Applicable

(2) Formulation, composition, or method of use patents

(i) Original declaration

The undersigned declares that Patent No. 5,616,346 covers the method of use of Diacol™ (sodium phosphate monobasic monohydrate, USP and sodium phosphate dibasic anhydrous, USP). formerly INKP-100. This product is the subject of this application for which approval is being sought: NDA # 21-097.

(ii) Amendment of patent information upon approval

InKine Pharmaceutical Company, Inc shall amend the original patent declaration by letter within 30 days after the date of approval of this application.

(3) No relevant patents – This section is not applicable

(4) Authorized signature

Martin Rose, M.D., J.D.
Senior Vice President,
Clinical Research and Regulatory Affairs
InKine Pharmaceutical Company, Inc.

4/26/99
Date

EXCLUSIVITY SUMMARY FOR NDA # 21-097 SUPPL # NA

Trade Name Visicol Generic Name sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous Tablets

Applicant Name InKine Pharmaceutical company, Inc. HFD # 180

Approval Date If Known _____

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 question 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:

_____

_____

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?

e) Has pediatric exclusivity been granted for this Active Moiety?

_____NO_____

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? (Rx to OTC switches should be answered NO-please indicate as such)

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 /___/ NO /_X_/

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

Comment: Sodium phosphate oral solution is available OTC under the monograph.

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# _____ _____

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 bicavailability 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 /___/ 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.

(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 /___/ 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 /___/ NO /___/

(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 /___/

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 /___/

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:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /___/

Investigation #2 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:

_____ _____

_____ _____

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 /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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"):

_____ _____

_____ _____

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 /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ 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 /___/

If yes, explain: _____

_____

/S/ 8-30-00

Signature Date

Title: Regulatory Health Project Manager

/S/ 9/20/00

Signature of Office/ Division Director Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

from hm paper archive
Vol 1.1
SD 11-22-99

Item 16: Debarment Certification

InKine Pharmaceutical Company, Inc (InKine) certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug. and Cosmetic Act in connection with this application.

On behalf of InKine Pharmaceutical Company, Inc.

Martin Rose, M.D., J.D.
Senior Vice President,
Clinical Research and Regulatory Affairs

10/29/99
Date

As required by the clinical protocols, all clinical investigators provided written certification that the Commissioner of the United States Food and Drug Administration had not notified them that they were ineligible to receive investigational drugs and/or participate in the clinical investigation of an unapproved drug.

During the course of the Phase III clinical investigation (protocol INKP-100-301), InKine determined that one of the participating investigators (Robert E. Morton, M.D.) had been placed on a "List of Restricted Investigators" as a result of deficiencies identified during a clinical investigation by the Division of Scientific Investigations between September 11, 1987 and October 23, 1987. As a result of this investigation, certain restrictions were placed on Dr. Morton pertaining to his future involvement and conduct of clinical research involving human subjects. Included in this list of restrictions was the stipulation that Dr. Morton would not conduct more than one clinical investigation concurrently. InKine discovered that Dr. Morton was an investigator in a hepatitis study at the site during his initiation and participation in the Diacol clinical trials.

Immediately upon confirming this investigator was conducting concurrent clinical studies, InKine terminated all study activity and participation with this investigator and requested an audit of the site and all clinical safety and efficacy data. Representatives from the Quality Compliance group at Premier Research Worldwide conducted this audit. Although the audit confirmed that Dr. Morton was adhering to Good Clinical Practices in accordance with the regulations and industry standards, InKine chose to terminate the Diacol clinical trial at this center. In addition, InKine provided written notification of this action to the Division Director on January 13, 1999 (please refer to IND Number [redacted]

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21097	**Trade Name:**	DIACOL (SODIUM PHOSPHATE DIBASIC ANHYDRA
Supplement Number:		**Generic Name:**	SODIUM PHOSPHATE DIBASIC ANHYDROUS/SODIU
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	Cleansing of the bowel as a preparation for colonoscopy, in adults 18 years of age or older.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
Tradename has been changed to Visicol.

Giving a pediatric waiver. 1. Visicol would not be used in a substantial # of peds patients (only appox 15,000 peds colonoscopies done per year). 2. There is currently NuLYTELY which is labeled for use down to 6 months. 3. Due to the number of tablets required for Visicol, compliance would bot be increased in children.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ALICE KACUBA

/S/ 8-30-00

Signature Date

CC:
NDA 21-097
HFD-180 Divisionfile

A.5. ENVIRONMENTAL ASSESSMENT

In accordance with 21 CFR 25.31 and FDA's current guidance document regarding the submission of an Environmental Assessment (EA), InKine claims a categorical exclusion from the requirement to submit an EA as part of the New Drug Application for Diacol Tablets since:

- The active ingredients, sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous, are not new molecular entities.
- Diacol Tablets are indicated as a purgative for bowel cleansing before performing colonoscopic procedures, the same indication as Fleet® Phospho®-Soda, a buffered aqueous solution available over-the-counter.
- FDA approval of this application will not introduce more sodium phosphate salt into the environment.

InKine further states that, to our knowledge, no extraordinary circumstances exist which could significantly affect the quality of the human environment if FDA approved this application.

Kacuba

MEMORANDUM OF TELECON

DATE: May 30, 2000

APPLICATION NUMBER: NDA 21-097, Diacol (sodium phosphate monobasic monohydrate, USP and sodium phospahte dibasic anhydrous, USP) Tablets

BETWEEN:

Name: Dr. Martin Rose, Senior VP of Regulatory Affairs
Mr. Steve Skiendzielewski, Executive Director, Manufacturing and Facility Operations
Phone: (610) 260-9361
Representing: InKine Pharmaceutical Company, Inc.

AND

Name: Alice Kacuba, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

BACKGROUND: NDA 21-097 was submitted on November 22, 1999 for the proposed indication as a bowel cleansing agent prior to colonoscopy. The chemistry review dated May 11, 2000, recommends an AE action, pending resolution of several chemistry issues. A discipline review letter was issued on May 24, 2000. Dr. Rose called requesting a clarification of the request for revised methods validation packages. Dr. Rose wanted to know how the methods validation packages did not meet the format of the Guideline for Submitting Samples and Analytical Data for methods Validation, February 1987. After checking with Dr. Al-Hakim, the review chemist, I called Dr. Rose back with the following information.

TODAY'S PHONE CALL: I called Dr. Rose and provided the following information:

1. Submit 4 copies of the methods validation packages (1 archival copy and 3 copies), each should be individually bound and ready to be sent to the FDA labs.
2. Each method should be listed by name, followed by the method validation. Dr. Rose said that the only two submitted were the only ones that were non-compendial. I suggested that he clearly list that in the resubmission; the method and say that it was a compendial test, thus no method validation is included.,
3. I gave an example on Page 27, where the reader is referred back to a previous section. I requested that the revised methods validation package provide all the needed information in each section and not refer the reader back to a previous section.

They said that they would take this information into consideration and would call back if they had further questions.

The call was concluded.

6·6·00

Alice Kacuba
Regulatory Health Project Manager

cc:
Archival NDA 21-097
HFD-180/Division File
HFD-180/A.Kacuba

Drafted by: A.Kacuba/May 30, 2000
Final: AK/June 6, 2000

TELECON

KPC-1a

MEMORANDUM OF TELECON

JUN 13 2000

DATE: June 13, 2000

APPLICATION NUMBER: NDA 21-097, Diacol (sodium phosphate monobasic, hydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets

BETWEEN:

Name: Dr. Martin Rose, M.D., J.D., Senior VP, Clinical & Regulatory Affairs
Phone: 610-260-9361
Representing: InKine Pharmaceutical Company, Inc.

AND

Name: Ms. Alice Kacuba; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

BACKGROUND: NDA 21-094, Diacol (sodium phosphate monobasic, hydrate, USP and sodium phosphate dibasic anhydrous, USP) Tablets was submitted on November 22, 1999 as a bowel cleansing agent prior to colonoscopy.

TODAY'S PHONE CALL: Dr. Martin Rose asked if InKine could submit a meeting request to discuss the division's thoughts on QTc prolongation in relation to the Diacol application. I told Dr. Rose that it may be premature to request such a meeting at this time as the review of the application is not complete. The 10 month user fee goal date for this application is September 22, 2000. In the case that the firm does submit a meeting request, I referred Dr. Rose to the guidance document entitled "Guidance for Industry; Formal Meetings with Sponsors and Applicants for PDUFA Products, February 2000" and to MaPP 4512.1, entitled "Formal Meetings Between CDER and External Constituents, 1996". Both of these documents are available on the Agency's web page.

The call was concluded.

/S/ 6-13-00

Alice Kacuba
Regulatory Health Project Manager

cc: Original NDA 21-097
HFD-180/Div. File
HFD-180/A.Kacuba
HFD-180/L.Talarico
HFD-180/S.Aurecchia
HFD-180/H.Gallo-Torres
HFD-180/R.Prizont
Drafted by: A.Kacuba/June 13, 2000
Final: AK/June 13, 2000

TELECON

MEMORANDUM OF MEETING MINUTES

Meeting Date: July 18, 2000
Time: 10:30am -12 noon
Location: Parklawn Building, 3rd floor, Conference room "C"

Application: NDA 21-097, sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous tablets

Type of Meeting: Type C meeting

Meeting Chair: Dr. Steve Aurecchia

Meeting Recorder: Ms. Alice Kacuba

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Steven Aurecchia, M.D.; Deputy Division Director
Hugo Gallo-Torres, M.D., Ph.D.; Medical Team Leader
Scheldon Kress, M.D.; Medical Reviewer
Jasti Choudary, B.V.Sc., Ph.D.; Pharmacology Team Leader
Tamal Chakraborti, Ph.D.; Pharmacology Reviewer
Alice Kacuba, R.N., MSN; Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

Sandip Roy, Ph.D.; Biopharmaceutics Reviewer

External Constituent Attendees and Titles:

InKine Pharmaceutical Company, Inc.

Leonard Jacobs, M.D.; Chairman and CEO
Marty Rose, M.D., J.D.; Sr. Vice President, Clinical Research and Regulatory Affairs
Barbara Nagel, M.D.; Vice President, Clinical Operations
Monroe Klein, Ph.D.; Vice President, Regulatory Affairs
Stephen Casey, M.B.A.; Vice President, Sales and Marketing

Consultants

Arthur Moss, M.D.; Professor of Medicine (Cardiology), University of Rochester School of Medicine
Stephen Steinberg, M.D.; Chief of Gastroenterology, North Shore University Hospital
Craig Aronchick, M.D.; Clinical Associate Professor of Medicine (Gastroenterology). University of Pennsylvania School of Medicine

Background: NDA 21-097 for sodium phosphate tablets was received on November 23, 2000 for the proposed indication as a bowel cleansing agent prior to colonoscopy at a dose of 60 grams, given in two divided doses, the evening before and the morning of the colonoscopy exam.

InKine has requested this meeting to discuss the data in the application relating to the observed transient electrolyte changes and resulting transient electrocardiographic (ECG) changes following the use of Diacol and Cherry Flavor NuLYTELY® in the Phase III studies.

Discussion Points: (Overheads presented by the firm are attached at the end)

After introductions were made, Dr. Aurecchia clarified the scope of the meeting: The Agency is willing to listen to the sponsor's interpretation of the data regarding the ECG changes seen in the clinical trials with Diacol. However, labeling would not be discussed, as the review of the application is still ongoing.

Dr. Rose summarized the dosing regimen used in the Phase III clinical trials (See Overhead # 1 and # 2). According to Dr. Rose:

- The Diacol™ dosing regimen for the Phase I and Phase III studies was comparable to that of sodium phosphate solution in terms of the dose of sodium phosphate and the timing of the dose.
- NuLYTELY® was dosed as recommended in its package insert.
- Electrolyte and ECG data comparisons between oral sodium phosphate and PEG/salt solution are confounded by the vastly different amounts of time between the last dose of the study drug and the data measurements.

The timeline for dosing is summarized in Overhead # 2:

The first dose of Diacol is at 6p.m. and the second dose is at 6a.m. Visit 1 is approximately 3-5 hours later, when ECG and blood samples were drawn prior to the colonoscopy exam. Visit 2 was 48-72 hours post colonoscopy when ECG and blood samples were obtained.

NuLYTELY was dosed according to the package insert. The dose was given between 3-10 p.m. Approximately 12 hours later, the colonoscopy was preformed after ECG and blood samples were obtained at Visit 1. Visit 2 was 48-72 hours post colonoscopy when ECG and blood samples were obtained.

Dr. Rose summarized the electrolyte data (See Overhead # 3). According to Dr. Rose:
- The expected transient serum electrolyte changes were observed following Diacol.
- Modest and transient changes in phosphorus, sodium, calcium, and potassium at the time of colonoscopy (Visit 1) were comparable to changes observed with sodium phosphate solution (increased phosphorus, decreased calcium. increased sodium, and decreased potassium).
- Changes resolved by Visit 2, 48 to 72 hours after colonoscopy.

Dr. Rose summarized the ECG data (See Overhead # 4). According to Dr. Rose:
- Transient QT prolongation was observed with oral sodium phosphate and PEG/salt solution at Visit 1. These changes resolved by Visit 2.
- With sodium phosphate, QT prolongation was secondary to changes in serum potassium and calcium, and unrelated to ion channel blockade.
  - -There was no effect of sodium phosphate on I_{Kr} in rabbit cardiomyocytes (Raymond Woosley, M.D., Ph.D.)
  - -Regression analyses of the Phase III data show a strong relationship between QT prolongation and reductions in serum calcium and potassium.

Dr. Rose summarized the cardiovascular adverse events (See Overhead # 5). According to Dr. Rose:
- No deaths or ventricular arrhythmias were reported in 548 patients who took sodium phosphate tablets.
- There was one brief run of ventricular tachycardia in a patient who took NuLYTELY (n=432).
- There is no evidence of increased risk of ventricular arrhythmias or sudden death in at least 10 million patients who have received sodium phosphate as a colonoscopy prep (during more than 100 years of marketing experience).

According to Dr. Rose, the firm's conclusions are (See Overhead # 6 and # 7):
- The cardiovascular risk of oral sodium phosphate colon cleansing agents is the risk of modest and transient hypokalemia.
- The available data indicate that this risk is undetectable in an experience of at least 10 million patients.
- There is no evidence of an increased rate of cardiovascular events with acute administration of oral sodium phosphate.

- Nonetheless, InKine believes that certain risks should be communicated to physicians:
  - -"Precaution: Oral sodium phosphate should be used with caution in patients with uncorrected hypokalemia or those taking digitalis preparations. In clinical studies, sodium phosphate use was associated with transient and generally modest reductions in serum levels of potassium."

Dr. Moss (who voluntarily disclosed that he has no conflict of interest in this matter) summarized

the baseline QTc characteristics of the subjects (See Overhead # 8).

Dr. Moss explained that a QTc measurement over 500 msec would be of concern and associated with arrhthmias. According to Dr. Moss, one patient at the Visit 1 (time of colonoscopy exam), in the Diacol treatment group had a QTc measurement between 500-509 msec (See Overhead # 9).

According to Dr. Moss, no patient had a QTc measurement over 489 msec at Visit 2, 49-72 hours post colonoscopy (See Overhead # 10).

Dr. Moss referred the review team to the submitted study report on the effect of sodium phosphate on I_{Kr} in rabbit cardiomyocytes.

According to Dr. Moss, there is a negligible risk for arrhthymias when sodium phosphate was used as a bowel cleansing agent.

Dr. Gallo-Torres asked for more information on the one patient in the Diacol group who at Visit 1, had a QTc measurement between 500-509 msec. Dr. Rose presented the following data:

	Baseline	Visit 1	Visit 2
Potassium	4.0	2.9	4.2
Calcium	8.4	7.3	8.4
QTc	440	506	463

Dr. Aurecchia inquired about the range of changes in potassium levels from baseline to Visit 1. Dr. Rose presented the following data:

-the maximum decrease in potassium was 2.7 mEq/L
-the maximum increase in potassium was 1.1 mEq/L

Dr. Rose presented Overhead # 11, which included information on electrolyte mean changes from screening visit to Visit 1 and to Visit 2 for studies 301 and 302.

Dr. Steinberg, (an investigator for one of the Phase III studies, who stated that he had nothing to disclose regarding conflict of interest in this area) emphasized the importance of the role of screening in the detection of colon cancer. Dr. Steinberg provided a historical perspective on the improvements in the screening process: better sedation, improvements in scope technology, and virtual colonoscopy. Despite these improvements, compliance with bowel cleansing remains an obstacle. According to Dr. Steinberg, if Diacol is singled out for QT prolongation, gastroenterologists will resist using this product, which will adversely affect colon cancer screening since patients have an aversion to the unpleasant taste of the current marketed agents.

Dr. Steinberg mentioned that routine monitoring during colonoscopy include continuous ECG and

pulse oximetry monitoring according to the American Society of Gastrointestinal Endoscopy (ASGE). Dr. Steinburg responded to a question from Dr. Kress, if this continuous monitoring was done when colonoscopies are conducted in venues outside of hospitals. According to Dr. Steinberg, yes, these safety procedures are followed. Dr. Gallo-Torres inquired if it was routine for a patient to have a screening ECG prior to having a colonoscopy. Dr. Steinberg summarized that the guidelines from ASGE indicate that for most normal individuals, it is not necessary to measure electrolytes or ECG prior to colonoscopy. Dr. Gallo-Torres inquired if the Diacol NDA included information on the adherence to ASGE guidelines. Dr. Gallo-Torres recommended that InKine amend the NDA and make a case, which includes the safety monitoring guidelines from ASGE that are followed during colonoscopy. InKine agreed to do this.

Dr. Aurecchia inquired about the compliance with the ASGE guidelines. Dr. Steinberg responded that a recent survey (source not quoted) found that 90-95% of physicians say that they follow the ASGE guidelines.

Dr. Aurecchia inquired about the electrolyte status of the 75 patients cited in the March 22, 2000 submission, who had a QTc change from baseline and measurements on treatment above 450 msec. According to Dr. Rose, this cohort was not analyzed but agreed to amend the application with that information. In response to a question from Dr. Rose as to whether that amendment would extend the review clock. Dr. Aurecchia responded that it would not extend the review clock.

Dr. Klien asked if the Division agreed with the proposed Precaution statement for the labeling that Dr. Rose presented earlier (See Overhead # 7). Dr. Aurecchia reiterated that it was premature to discuss labeling at this time, as the review of the application was ungoing. The statistical and clinical reviews need to be finalized before any labeling can be discussed. Dr. Klien asked if the Division agreed in principle to InKine's approach to the labeling. Dr. Aurecchia agreed, in principle, to the approach.
Dr. Gallo-Torres asked Dr. Moss his opinion on the need for JT measurement in this situation. Dr. Moss responded that, in this case, there was no widening of the QRS complex, so there is no issue with the JT interval.

Minutes Preparer: /S/ 8-8-00

Chair Concurrence: /S/ 8/8/00

Attachments:

SEP - 7 2000

MEMORANDUM

DATE: September 6, 2000

FROM: Steven Aurecchia, MD
Deputy Director, Division of Gastrointestinal and Coagulation Drug Products

TO: NDA 21-097

SUBJECT: Summary of Review Issues and Recommendation

Administrative

NDA 21-097 for Visicol™ (sodium phosphate monobasic monohydrate and sodium phosphate dibasic anhydrous) Tablets was submitted by InKine Pharmaceutical Company on November 22, 1999. It is intended for use as a bowel cleansing agent in preparation for colonoscopy in adults 18 years of age or older. The application was assigned a standard review. The 10-month PDUFA date is September 23, 2000.

Clinical/Statistical

Two phase III trials support the efficacy and safety of Visicol™. Both were randomized, parallel-group, multicenter studies designed to demonstrate equivalence in colon cleansing between Visicol™ and a commercially available purgative product (NuLYTELY). A total of 859 adult patients were enrolled and treated. Males and females were about equally represented. Approximately 87% of the study population were Caucasians and 34% were over age 65. In both trials, there was no statistically significant difference between treatment groups in the primary efficacy variable, overall quality of colonic purgation measured colonoscopically on a validated 4-point scale (the 95% confidence intervals were within the pre-established range). Results were also consistent for the secondary efficacy variable, the quality of colonic purgation in the ascending colon. The principal weakness in the data and the statistical efficacy argument relates to compliance. As reported in the patient questionnaire, the entire dose of study product was ingested by significantly fewer NuLYTELY subjects than Visicol™ subjects. This finding precludes a strict claim of equivalent efficacy. In addition, both trials were effectively unblinded by the occasional presence of undigested or partially digested Visicol™ tablets. The impact, if any, of this unblinding as a potential source of physician (investigator) bias is unclear.

Two principal safety issues were identified during the course of review: the colonoscopic finding of superficial mucosal apthous ulcerations and QTc prolongation on ECG in a subset of study patients. The frequency of observed ulcerations was greater with Visicol™ than with NuLYTELY by a statistically significant margin. The clinical significance of this finding, if any, is unclear. Similarly, QTc prolongation occurred with a significantly greater frequency in subjects who received Visicol™. This ECG finding correlated with changes in serum potassium and calcium and does not appear to be a direct effect of the drug on cardiac conduction. In rabbit cardiomyocytes, sodium phosphate does not produce ion channel blockade.

Pharmacology/Toxicology

No new preclinical studies were submitted in support of this application. There are no literature reports regarding the preclinical oral toxicity of dibasic sodium phosphate/monobasic sodium phosphate combinations. Available animal data on the individual phosphates was submitted and reviewed, albeit of limited relevance to the safety of Visicol™.

The application is nonetheless approvable from a pharmacology/toxicology perspective, particularly in view of the available literature on the absorption, distribution, metabolism and excretion of phosphates in humans and the extensive clinical experience with sodium phosphate solution.

Certain changes and additions will be incorporated into the preclinical section of the sponsor's proposed labeling.

Chemistry, Manufacturing and Controls

Please refer to Dr. Al-Hakim's detailed review of the CMC section of this application. The sponsor proposes to market tablets containing 1.5 grams of sodium phosphate (1.102 grams sodium phosphate monobasic monohydrate, USP and 0.398 grams sodium phosphate dibasic anhydrous, USP). The information provided is acceptable for the drug substance, drug product and packaging materials. The stability data were generated under ICH storage conditions and support an initial expiry of 12 months. All establishment reviews are acceptable.

The application is approvable from a CMC perspective with modifications to the proposed CMC sections of the labeling.

Clinical Pharmacology and Biopharmaceutics

Adequate data has been presented to characterize the concentration-time curves for serum inorganic phosphorus following administration of Visicol™. Kinetic parameters have been described for males and females and geriatric patients. The effect of renal dysfunction on Visicol™ pharmacokinetics was not studied; however, since ionized inorganic phosphate is excreted almost exclusively by the kidneys, caution is warranted when using this product in patients with renal insufficiency. Visicol™ is not expected to be metabolized by the liver.

[redacted]

With the foregoing as a Phase IV commitment and labeling clarifications, the application is approvable from a Biopharmaceutics standpoint.

Pediatrics

A pediatric waiver has been granted. Visicol™ would not be used in a substantial number of pediatric patients, as colonoscopy is not frequently performed in this population. In addition, NuLYTELY is labeled for use down to 6 months of age, and may be more appropriate as a liquid formulation.

Data Integrity

The Division of Scientific Investigations audited three clinical study sites and found only minor violations of good clinical practice standards. These deficiencies do not adversely impact the acceptability of the data submitted in support of this NDA.

Labeling and Nomenclature

The currently proposed proprietary name Visicol™ is acceptable to OPDRA and the Division.

The draft labeling as submitted by the sponsor is not acceptable. In brief, the Description section of the package insert requires clarification. The Clinical Pharmacology section needs both clarifications and addition of information on special populations. The Clinical Studies section should emphasize efficacy comparable, but not equivalent to the PEG salt solution comparator. The Contraindications, Warnings and Precautions sections are both incomplete and inconsistent with the current professional labeling for OTC sodium phosphate containing products (63 FR 27886). The Adverse Events section should more accurately reflect the safety profile of Visicol and should avoid comparisons with the PEG salt solution due to potential biases. Additionally, the Dosage and Administration section needs clarification.

Conclusion

The Division recommends this NDA be APPROVED with revised labeling acceptable to the Agency. The above reference Phase IV commitment will be reiterated in the action letter.

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