CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18956/S28

MEDICAL REVIEW(S)

ORIG

401

DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

JAN 16 1992

NDA: 18-956/S-028

Date Received: January 11, 1990 Review Date Completed: March 16, 1990

Date Assigned: January 16, 1990

APPLICANT: Sterling Drug Inc.
Sterling Research Group
9 Great Valley Valley Parkway
Malvern, PA 19355

TYPE OF SUPPLEMENT: Efficacy Supplement - New Indication for use of Omnipaque Injection administered orally or rectally in children for examination of the gastrointestinal tract.

NAME OF DRUG: Omnipaque Injection (iohexol) 180, 240 and 300 mgI/mL

REVIEWER: Silas Chow, M.D.

TABLE OF CONTENTS

BACKGROUND:

Omnipaque Injection, (iohexol), was originally approved in December 1985 by the Food and Drug Administration. At that time, it was one of two nonionic radiocontrast agents intended for various intravascular and intrathecal indications in adults. Supplemental approval has been obtained over the years to include intravascular and intrathecal use in children, various body cavity indications and also for oral use for gastrointestinal imaging in adults. The following indications are currently approved:

Adult Intrathecal	Adult Intravascular
Cervical Myelography	Excretory Urography
Thoracic Myelography	Peripheral Venography
Lumbar Myelography	Peripheral Arteriography
Total Columnar Myelography	Cerebral Arteriography
Computerized Tomography of Head and Spine	Angiocardiography
	IV and IA-DSA
	CT of Head and Abdomen
	Visceral Arteriography
Pediatric Intravascular	**Adult Body Cavities**
Angiocardiography	Arthrography
Excretory Urography	ERP/ERCP
Voiding Cystourethrography	Hysterosalpingography
Myelography	Herniography
	Oral Use

The current supplemental application provides for an expansion of the currently approved indications for Omnipaque Injection. In addition to various intravascular and intrathecal uses, Omnipaque Injection is currently approved for oral administration to an adult patient population for gastrointestinal imaging. The drug is also approved for various pediatric applications when administered intravascularly or intrathecally. At this time, approval is requested for the use of Omnipaque 180, 240 and 300 concentrations (providing 180, 240 and 300 mgI/mL, respectively) administered orally or rectally to children for examination of the gastrointestinal tract.

The applicant has not conducted controlled clinical studies using Omnipaque 240 for the new indication, but is relying on the adequacy of the studies conducted in the United States using both Omnipaque 180 and Omnipaque 300 to support its approval.

Based upon FDA's prior determination of Omnipaque's safety and effectiveness when administered orally to adults for gastrointestinal imaging, the applicant decided to seek approval for the same indication in children. Additionally, because oral administration may be difficult in the lower age groups, the applicant has also chosen to request approval for the rectal administration of Omnipaque for the same indication.

Water-soluble iodinated media such as Omnipaque are used clinically as an alternative to barium sulfate in radiographic examination of the gastrointestinal tract, especially in patients where gastrointestinal perforation is suspected or aspiration of the contrast agent is a possibility. It is known that barium salts are toxic if aspirated or leaked into the peritoneal cavity and there are animal and clinical data to demonstrate that water-soluble contrast media present a much lesser potential for toxicity upon aspiration and are readily absorbed from the peritoneal cavity.

Non-ionic contrast media such as Omnipaque may offer some advantages when administred intravascularly over conventional ionic media. Presumably, this advantage is due to the lower osmolality which is a characteristic of the non-ionic media, although data to support this presumption are inconclusive. This advantage was assumed by the applicant to be a possibility when clinical trials were planned for oral use of Omnipaque. The applicant also presumed that the lower osmotic potential of Omnipaque would result in a lesser degree of fluid shifts into the bowel upon administration when compared to that which occurs following the use of the ionic agents approved for oral use. Clinically, decreased incidence of diarrhea and potentially better visualization of the gastrointestinal tract should result with the use of Omnipaque. However, the controlled studies conducted in the United States in support of this application were not designed to address this issue since barium sulfate was used as the comparator and not a conventional ionic agent.

The data provided by the applicant demonstrate the safety and effectiveness of Omnipaque 180 and Omnipaque 300 for the requested indication. The European data supplied by the applicant support the inclusion of Omnipaque 240 for the indication.

REVIEW OF CLINICAL STUDIES

The studies presented by the applicant in this submission are described below:

Controlled and Uncontrolled Clinical Studies

Study	Investigators	Design	Iohexol conc.(mgI/mL) NO. of Patients			Barium Sulfate	Total
Domestic			140	180	300		
IOH-1058A	Mervyn Cohen, M.D. Indiana Univ. MC Indianapolis, IN	Randomized, double-blind comparison	4	27	17	22	70
IOH-1058B	Richard Towbin M.D. Children's Hospital of Michigan Detroit, MI	Nonrandomized, open study	3	12	4	-	19
			7	39	21	22	89

Foreign			Iohexol Concentrations (No.Pts) Missing	80	110	120	175	240	350
N-121	Gunnar Stake, M.D. Dept. of Radiology Rikshopitalet Oslo, Norway	An open, non-comparative trial	3	2	1	1	32	4	3

Total 46 patients

No clinical publications were submitted in support of this supplemental application.

REVIEW OF INDIVIDUAL CLINICAL TRIALS

United States Study (IOH - 1058)

A. Investigators

Center A

Mervyn Cohen, M. B., Ch.B.
James Whitcomb Riley Hospital for Children
Indiana University Medical Center
Indianapolis, IN 46223

Center B

Richard B. Towbin, M. D.
Children's Hospital of Michigan
Detroit, MI 48201

B. Objectives

1. To evaluate and compare the safety and tolerance of iohexol (180 and 300 mgI/mL) with barium sulfate during and after contrast examination of the GI tract in pediatric patients by measuring vital signs and recording the occurrence of adverse events (Part A).

2. To evaluate the safety, tolerability and efficacy of iohexol (140 and 180 mgI/mL) in patients undergoing contrast examination of the GI tract where barium is contraindicated (Part B).

C. Study Design

This Phase 3, two-center pediatric study of the gastrointestinal tract was conducted in two concurrent parts. The numbers of patients enrolled into each group at each center are as follows:

	Iohexol Conc. or Barium	Patients Enrolled Center-A	Center-B	Total Pts
Part-A (double-blind)	180 mgI/mL	17	4	21
	300 mgI/mL	17	4	21
	Barium Sulfate	18	4	22
Part-B (Open)	140 mgI/mL	4	3	7
	180 mgI/mL	10	8	18
	Total	66	23	89

1. Patient Population - A total of 89 patients were studied under the protocol IOH-1058 and received a contrast medium X-ray evaluation of the GI tract (66 at Center A and 23 at Center B).

   Demographics and Contrast Administration Information are summarized in the following tables.

   a. Demography (Part A)

Center A	Iohexol 180 mgI/mL	iohexol 300 mgI/mL	Barium Sulfate
Number of Patients	17	17	18
Sex (M/F)	9/8	10/7	13/5
Age, (mons)[a]	53.6±55.3 (3.9,194)	60.2±73.7 (1.2,203)	35.2±50.0 (1.4,182)
Weight, Kg[a]	19.5±19.0 (6.9,77.0)	18.7±17.8 (3.9,69.5)	15.3±12.7 (3.0,51.5)
Height, cm[a]	97.9±34.4 (58.4,183)	96.3±34.4 (61.0,162)	81.3±28.2 (31.0,143.5)

Center B	Iohexol 180 mgI/mL	iohexol 300 mgI/mL	Barium Sulfate
Number of Patients	4	4	4
Sex (M/F)	2/2	2/2	2/2
Age, (mons)[a]	67.5±76.7 (0.7,166)	81.6±49.8 (10.4,126)	70.3±73.1 (1.1,144)
Weight, Kg[a]	21.8±23.3 (4.5,56.0)	21.3±11.7 (10.2,35.0)	24.5±22.4 (2.5,53.0)
Height, cm[a]	102.2±48.1 (53.3,162)	114.2±29.2 (81.0,150)	97.8±40.8 (53.0,147.0)

Pooled	Iohexol 180 mgI/mL	iohexol 300 mgI/mL	Barium Sulfate
Number of Patients	21	21	22
Sex (M/F)	11/10	12/9	15/7
Age, (mons)[a]	56.2±58.0 (0.7,194)	64.3±69.2 (1.2,204)	41.6±54.5 (1.1,183)
Weight, Kg[a]	19.9±19.3 (4.5,56.0)	19.2±16.6 (10.2,35.0)	15.5±14.9 (2.5,53.0)
Height, cm[a]	98.7±36.0 (53.3,183)	99.7±33.6 (61.0,162.5)	84.3±30.4 (31.0,147.0)

a = Mean ± SD (Range)

b. Demography (Part B)

Center A	Iohexol 180 mgI/mL	iohexol 140 mgI/mL
Number of Patients	10	4
Sex (M/F)	5/5	3/1
Age, (mons)[a]	16.8±49.7 (0.5,158)	1.0±0.6 (0.1,1.4)
Weight, Kg[a]	3.8±6.9 (0.9,23.4)	2.5±1.3 (1.4,4.3)
Height, cm[a]	51.1±41.3 (33.0,168)	39.8±5.24 (35.0,46.0)

Center B	Iohexol 180 mgI/mL	iohexol 140 mgI/mL
Number of Patients	8	2
Sex (M/F)	4/4	2/0
Age, (mons)[a]	10.6±12.5 (0.2,32)	20.8±29.1 (0.2,41.4)
Weight, Kg[a]	5.8±2.9 (2.0,10.0)	9.6±7.6 (4.2,15.0)
Height, cm[a]	58.6±14.9 (35.0,77.0)	72.0±26.9 (53.0,91.0)

Pooled	Iohexol 180 mgI/mL	iohexol 140 mgI/mL
Number of Patients	18	6
Sex (M/F)	9/9	5/1
Age, (mons)[a]	14.6±37.2 (0.2,158)	7.6±16.6 (0.1,41.4)
Weight, Kg[a]	4.7±5.5 (0.9,23.4)	4.8±5.1 (1.4,15.0)
Height, cm[a]	54.2±32.6[b] (33.0,168.0)	50.5±20.9 (35.0,91.0)

Contrast Administration Information - Part A

Grouping	iohexol (mgI/mL) or barium	Number of patients	Total Volume (mL)a	Total Dose (mL/kg)a
Center A	180	17	67.1±51.6 (15.0,240)	5.2±6.4 (1.1,29.3)
	300	17	69.7±58.8 (20.0,276)	5.8±6.2 (1.6,25.8)
	Barium	18	67.4±42.0 (15.0,200)	6.7±3.5 (0.8,13.3)
Center B	180	4	72.0±67.0 (28.0,170)	5.1±4.1 (1.1,10.4)
	300	4	297.5±370.4 (60.0,850)	11.9±9.1 (4.6,24.3)
	Barium	4	121.5±126.2 (25.0,300)	5.8±3.0 (3.5,10.0)
Pooled	180	21	68.5±53.0 (15.0,240)	5.2±5.9 (1.1,29.3)
	300	21	113.1±178.2 (20.0,850)	7.0±7.0 (1.6,25.8)
	Barium	22	77.2±64.5 (15.0,300)	6.5±3.3 (0.8,13.3)

Contrast Administration Information - Part B

Grouping	iohexol (mgI/ml)	No.of Pts.	Total Volume (mL)a	Total Dose (mL/kg)a
Center A	180	10	30.4±53.3 (5.0,180)	8.8±4.8 (3.9,20.2)
	140	4	25.8±29.6 (8.0,70.0)	8.6±5.2 (5.0,16.2)
Center B	180	8	47.6±21.1 (20.0,80.0)	9.7±6.7 (5.3,25.9)
	140	2	82.5±53.0 (45.0,120)	9.4±1.9 (8.6,10.7)
Pooled	180	18	38.1±42.0 (5.0,180)	9.2±5.6 (3.9,25.9)
	140	6	44.7±44.1 (8.0,120.0)	8.9±4.1 (5.0,16.2)

a = Mean ± SD (Range)

Sponsor's Description

In Part A, Center A gave consistent total volumes across the 3 dose groups. Center B gave considerably more iohexol 300 mgI/mL compared to the iohexol 180 mgI/mL and barium groups. In Part B, Center A also gave consistent total volumes across the 2 dose groups. At Center B, about twice the total volume of iohexol 140 mgI/mL was administered compared to iohexol 180 mgI/mL.

Reviewer's Comment

No disagreement with the sponsor's analysis.

High Risk Patients - (sensitivity to allergens and/or medications)

A total of 21 of 42 (50%) iohexol patients and 16 of 22 (73%) barium patients from Part A and 20 of 24 (83%) iohexol patients from Part B had at least one risk factor.

Dropouts, Withdrawals and Exclusions

No patients at either center were dropouts, except one patient B0180, in violation of the protocol, received iohexol 140 mgI/ml from the study supplies for a CT examination to observe a suspected leak of a recent anastomotic repair within 48 hours of the study procedure. Therefore, this patient was excluded from all analyses.

Patients A0020, A0230 and B0190 were excluded from vital sign and adverse event analyses because they had non-diagnostic procedures requiring intervention with a second contrast medium.

Safety Results - (Sponsor's description)

Vital signs - Supine systolic and diastolic blood pressures and pulse rate were obtained, within 4 hours prior to and at 1, 6 (for inpatients only) and 24 hours after contrast medium adminstration.

The mean values for these parameters were compared by dosage group, center and overall and were generally comparable with slight transient changes over time. The mean maximum increases and decreases in vital signs across the 2 centers for the 4 dosage groups were no greater than:

	Vital Sign Changes (mmHg/bpm)		
Concentration (mgI/ml)	Systolic Pressure	Diastolic Pressure	Pulse Rate
iohexol 140	± 8	± 8	±18
iohexol 180 (Part A)	± 3	± 5	±12
iohexol 180 (Part B)	± 9	± 8	±12
iohexol 300	± 6	± 3	± 5
Barium	± 7	± 4	±10

Nine (9) patients had systolic blood pressure changes of ± 30 mmHg or greater (ranged from -38 to +63 mmHg). Three (3) patients had diastolic blood pressure changes of ± 30 mmHg or greater (ranged from +30 to +38 mmHg). Twenty-one (21) patients had pulse rate changes of ± 30 bpm or greater (ranged from -64 to +98 bpm).

A four month-old boy (O.P.D. patient) A0480 experienced a pulse rate increase of 98 bpm one hour post iohexol administration. His baseline pulse rate was unusually low at 56 bpm. At 4 hour, the pulse rate was 127 bpm but no 6 or 24-hour follow-up. Baseline blood pressure was 105/60 mmHg which increased to 106/90 mmHg at one hour post procedure and remained stable at 116/74 mmHg at 4 hours post contrast administration.

Reviewer's Comment

No disagreement with the sponsor's analysis. Four (A020, A230, B180, B190) of these 67 iohexol patients were excluded from the vital signs analysis. Among which one patient (A230) who received iohexol-180 mgI/ml experienced a mild systolic hypertension and the other patient (B190) who received iohexol-140 mgI/ml experienced mild-moderate hypotension. It is interesting to note that the pulse rate of the third patient (A020) who received iohexol-300 mgI/ml had a similar reading with diastolic blood pressure at pre- and post-contrast (one hour) observation which I am not convinced (see table below).

Patient	Baseline(mmHg) 4-H prior	1 hour	6 hours	24 hours	Maximum value	Minimum value
A230	(110)	(134)	-	-	(34)	(34)
	82/60	105/60	-	-	23/0	23/0
B190	(140)	(142)	(120)	(140)	(2)	(-20)
	86/68	67/48	56/34	65/49	-19/-19	-30/-34
A020	(65)	(68)	-	-	(3)	(3)
	105/65	105/68	-	-	0/3	0/3
A610	(160)	(128)	(128)	(126)	(-32)	(-34)
	90/60	78/?	52/32	68/48	-12/-12	-38/-28

One another patient (A610-iohexol-300) experienced a persistent mild to moderate hypotensions lasted for 24 hours.

Note: Opacification of the GU tract was observed in one patient (A660 iohexol-140).

Taste/Tolerance (sponsor's description)

At each center, the orally-administered contrast medium was routinely given undiluted. At Center B, powdered drink mix was added to the iohexol (180 and 300 mgI/ml) for 5 patients for enticement purposes. Patient B0050 would not drink contrast medium unless V-8 Juice was added. Most patients at both centers could not evaluate the taste of the orally administered contrast medium owing to their young age.

Adverse Events (sponsor's description)

In Part A (double-blinded), eleven (11) patients from the iohexol-180 mgI/mL group had a total of 17 adverse events and nine (9) patients from the iohexol 300 mgI/mL group had a total of 14 adverse events. Only one patient from the barium group had a single adverse event (vomited). The most frequently occurring adverse events were diarrhea 10 of 20 (50%) in iohexol-180 group versus 9 Of 20 (45%) with iohexol-300 group. In Part B (open nonrandomized), three (3) iohexol 180 mgI/ml patients had one adverse event each. Two patients had diarrhea (11%) and one vomited. The following table shows the distribution of adverse events, the study part at which they occurred, and the relation to drug administration.

Summary of Adverse Events

		iohexol (mgI/mL)		
Adverse Events	140	180	300	Barium
Part A				
No. of Pts. (%)	NA	20	20	22
Diarrhea		10 (50%)	9 (45%)	-
Vomiting		3 (15%)	-	1
Fever		1	2 (10%)	-
Nausea		1	2 (10%)	-
Hypotension			1	-
Hives		1	-	-
Abdominal Pain		1	-	-
		17	14	1

Part B No. of Pts. (N)	5	18	NA	NA
Diarrhea	-	2 (11%)		
Hypotension	1			
Vomiting	-	1		
Aspiration	1			
	2	3		

Reviewer's Comment

The most commonly reported events in both drug groups were diarrhea (48% in the Part A versus 11% with Part B) and no explanation was given by the sponsor why the results of this adverse event were vastly different from one part to another in a same protocol? However, none of the Barium group patients experienced diarrhea.

None of these events were persistent in nature and all patients recovered without sequelae.

Efficacy Results

The quality of contrast enhanced radiographs for each organ imaged, and the overall procedure were assessable for 87 of the patients studied. The overall data are shown below:

	Barium	iohexol (mgI/ml)		
Part A	Sulfate	140	180	300
Excellent	12	NA	4	7
Good	10		14	12
Poor	-		3	2
Part B				
Excellent		1	6	
Good		4	12	
Poor		-	-	

Sponsor's Description

Overall assessments for radiographic visual quality, density and mucosal coating were satisfactory (graded as good and excellent). There is a significant difference between contrast media due to the greater frequency of excellent assessments in the barium group versus iohexol groups. There was no statistically significant difference between the contrast groups (iohexol 180 mgI/mL and 300 mgI/mL) in Part A with regard to diagnostic versus nondiagnostic assessments. Five patients (3, iohexol 180, 2 iohexol 300 group) were graded as nondiagnostic values. In Part B, the overall quality assessments of radiographic visualization for both iohexol concentrations (140, 180 mgI/mL) were diagnostic in all procedures.

Reviewer's Comment

No disagreement with the sponsor's analysis.

Reviewer's Evaluation and Overall Summary of U.S. Phase 3 Study

This Phase 3, two-center pediatric GI study was conducted in two concurrent parts (Part A double-blind, Part B open). Contrast media were administered orally and by rectal and enteric tube to 89 (including 4 violators) pediatric patients from about one day to 17 years of age and from less than one kilogram to about 77 kg body weight.

In Part A of a two part, two center study, iohexol at concentrations of 180 and 300 mgI/mL was compared to barium sulfate in a randomized, double-blind manner to assess its safety and efficacy during pediatric GI examinations. The total volumes administered for iohexol 180 and 300 mgI/mL were from 15-240 mL and from 20 to 850 mL, respectively. The range for barium was from 15-300 mL. Mean volumes were 68 mL for iohexol-180, 113 mL for iohexol-300 and 77 mL for barium sulfate.

In Part B, iohexol at concentrations of 140 and 180 mgI/mL was evaluated in an open, nonrandomized manner to assess its safety and efficacy in barium contraindicated pediatric patients during GI examinations. The total volumes administered for iohexol-140 and iohexol-180 were from 8-120 mL, and from 5-180 mL, respectively. Mean volumes were 45 mL for iohexol-140 and 38 mL for iohexol-180. Both demographic and contrast administration data were generally comparable between drug groups and across centers.

Safety Results

With respect to drug tolerance, no serious adverse effects were encountered in the patients studied.

Fourteen of 38 (37%) patients who received iohexol-180 mgI/mL and 9 of 20 (45%) patients who received iohexol-300 mgI/mL experienced a total of 20 and 14 adverse events, respectively. Only one barium sulfate patient experienced vomiting during oral consumption of contrast medium. The most frequently occurring adverse events in both drug groups were diarrhea 12 (32%) in iohexol-180 versus 9 (45%) with the iohexol-300 group. The diarrhea was mild to moderate in intensity and lasted for 12 hours. The overall incidence of diarrhea in the iohexol group was 21 of 58 (36%) whereas none with the barium sulfate group.

Efficacy Results

The overall quality of radiographic visualization was judged satisfactory (excellent or good) for 92% and 90% for iohexol-180 and iohexol-300, respectively. The media appear to be comparable in this respect. However, there was a difference between Omnipaque and barium sulfate as contrast media due to the greater frequency of excellent assessments in the barium sulfate group versus iohexol groups.

Comment

Although the study is relatively small, I agree that it is supportive of the sponsor's claims that iohexol is safe and effective for this purpose. It is interesting to notice that the trend of more adverse events in Part-A than in Part-B.

SUPPORTIVE DATA - STUDY N-121

Investigator: Gunnar Stake, M. D.
Pediatric Radiology Department
Rikshospitalet
Oslo, Norway

This was a Phase 2/3 open, noncomparative study of iohexol used for examination of the gastrointestinal tract in pediatric patients. A total of 46 patients (30 patients entered into the main study and a pilot study with 16 patients) were successfully completed at one center. Oral informed consent was obtained from each patient's parents or legal guardian prior to enrollment into the study.

Omnipaque (Pilot Study) was given to 16 patients (9 males and 7 females), ranging in age from less one to 56 months (mean 7 months) and weighing 3-15 kgs (mean 5.2 kgs). Iohexol (Main Study) was given to 30 patients (19 males and 11 females), ranging in age from less one to 167 months (mean 35.6 months) and weighing 3-40 kgs (mean 11.4 kgs).

In the pilot study, iohexol was given to the 16 patients at 6 different concentrations ranging from 80 to 350 mgI/ml. In the main study 27 examinations were performed using 8-225 ml of iohexol-175 mgI/ml and 3 examinations used 12-20 ml of the 350 mgI/ml concentration. The mean volume for all examinations with 175 mgI/ml was 53.2 ml and the mean dose was 6.4 ml/kg (range from 0.4-14.3 ml/kg).

Overall, the route of administration was by NG tube in 29 examinations, orally in 14 and rectally in 3.

No patient dropped out or withdrew from the study or was excluded from data analysis (stated by the sponsor).

Efficacy Results

The quality of radiographic visualization for all film series evaluated in both pilot and main study was graded as good and excellent. The transit time of contrast medium to the cecum was recorded in only 15 examinations and varied from 18 to 270 minutes (mean 77.2 minutes).

Taste Acceptability - Only 18 of 30 patients in the main study evaluated taste acceptability (see table below).

neutral	3
less good	5
not acceptable	2
no remarks (CM received by tube)	8

None of the patients in the pilot study were able to assess taste acceptability because of their young age and/or the route of administration.

Reviewer's Comment

No disagreement with the sponsor's ananlysis.

Safety Results

There were no adverse events reported in this study.

Reviewer's Evaluation and Comment

This is an open, noncomparative study. A total of 46 patients was entered into the study in two-part (pilot study 16, main study 30) at one center.

N - 121 (exclude 3 repeaters)

	Oral	Tube	Rectal	Total Pts.
Pilot Study (N-16)	3	12	1	16
Main Study (N-30)	11	17	2	30
	14	29	3	46

Volume Dose (mL) / Examination

mgI/mL	10	10	15	20	30	35	40	50	60	75	100	180	200	225	Total
Pilot Study		1		1					(pt. #140 with unknown dosage)						2
80							1		1						2
110							1								1
120									(pt. #010 with unknown dosage)						-
175		1		3			1								5
240	3	1													4
	3	3		4			3		1						14
Main Study															
175	1	1	2	2	1	1	10	2	1	1	2	1	1	1	27
350			2	1											3
	1	1	4	3	1	1	10	2	1	1	2	1	1	1	30

Contrast medium was administered orally, rectally or by NG tube at concentrations ranging from 80-350 mgI/ml and at volumes ranging from 2-225 mL depending on age and weight.

Results

No adverse events were reported. The quality of radiographic visualization was optimum for all of the patients studied, except for one examination (#0160) was missing in the pilot study. Both vital signs and laboratory measurements were not done?

Comment - I am not convinced that in this open clinical trial conducted by Dr. G. Stake Oslo, Norway had no single incidence of adverse event reported (such as diarrhea?). No safety measurements (vital signs and laboratory work) were performed in this clinical trial. It appears to me that the study is inadequate and meaningless to serve as a basis for approval, but the data may be considered supportive, especially with respect to the rectal route of administration.

OVERALL SUMMARY AND CONCLUSIONS

Two studies (one U.S. and one European), were completed using iohexol for imaging of the GIT by conventional x-ray techniques in pediatric patients.

One domestic study (IOH-1058), was a Phase 3 clinical trial conducted at two centers in the United States. The study was divided into two parts. The first part (A) was a double-blind comparison of iohexol at 180 and 300 mgI/mL and barium sulfate. The second part (B) was a nonrandomized, open study of iohexol at 140 and 180 mgI/mL concentrations in patients in whom barium was contraindicated. The other study (N-121), was conducted by Dr. Stake in Oslo, Norway and was monitored by Nycomed A/S. (This trial consisted of a pilot study where iohexol was administered at 6 different concentrations ranging from 80-350 mgI/mL and a main study where iohexol was administered at either 170 or 350 mgI/mL).

Safety Results

With respect to drug tolerance, no serious adverse events were encountered in the patients studied. However, a main concerns is the incidence of diarrhea which occurred in a high percentage of both adult and pediatric studies (see table below):

	Adverse Event Followed By Oral (GIT) Contrast Agent		
Adult Study (Approved)	iohexol-180 (mgI/mL)	iohexol-300 (mgI/mL)	iohexol-350 (mgI/mL)
P-633 (Ph-I) Study			
Dose range: Mean±SD (gI)			150 ml (52.5 gI)
Diarrhea			10/11 (91%)
PS-632 Study (Dr. Enge)			
Dose range: Mean±SD (gI)			50-100ml (35gI)
Diarrhea			23/30 (76%)
N-137 Study (Dr. Enge)			
Dose range: Mean±SD (gI)			100ml (35gI)
Diarrhea			1/24 (4.3%)
Pooled (PS-632,N-137)			
Diarrhea			24/54 (45%)

The safety data from these three studies support the conclusion that the incidence of diarrhea with Omnipaque is greater than that observed with barium sulfate. The incidence of diarrhea should be reflected in the package insert.

Pediatric Study (Current Submission)	iohexol-180 (mgI/mL)	iohexol-300 (mgI/mL)	iohexol-350 (mgI/mL)
IOH-1058 (Part-A Study)			
Dose range: Mean±SD (gI)	15 - 240 mL (68.5±12.3 gI)	20 - 850 mL (113±34 gI)	
Diarrhea	10/20 (50%)	9/20 (45%)	
IOH-1058 (Part-B Study)			
Dose range: Mean±SD (gI)	5 - 180 mL (38±6.8 gI)		
Diarrhea	2/18 (11%)		
Pooled (Part A and B)			
Diarrhea	12/38 (32%)	9/20 (45%)	
Pooled Again (Conc. 180/300)			
Diarrhea		21/58 (36%)	

Based on the results reported herein, this reviewer believes that there is a direct relation between dose and toxicity; as the total dose and concentration increase, the frequency and severity of diarrhea also increases.

The sponsor provided no clinical analysis regarding the patients involved with large bowel study (see reviewer's table below).

Large Bowel Examination (By rectal tube)

	180 mgI/ml	300 mgI/ml	Barium	Total
Center A	A330 A070	A200 A290 A440	A100	6
Center B	B230	B070		2
	3	4	1	8

5 of 43 (12%) Center A patients had large bowel study compared with 10% in the Center B. Only one patient in the Center A group had diarrhea reported.

Other Observations

The fact that the urinary tract was visualized in one patient (A0660) suggests that there was either a leak of the contrast medium followed by absorption from the peritoneum or that there is some degree of absorption upon oral dosing (according to pharmacokinetic and excretion study that the mean amount of iohexol excreted in urine as a percentage of dose was 0.3%). This is an interesting finding, but does not relate to the safety or effectiveness of the drug for the requested indication.

actually fluid left in from intestinal (cellular extravascular) space into the vascular compartment

Again, the hematology, serum and urine measurements were not made in this submission. Therefore, the extent of the fluid shift from the intracellular and interstitiial space into the intravascular compartment cannot to determined.

The sponsor in volume 1, page 62, second paragraph makes the following statements regarding that "Nonionic media (iohexol) offer significant safety advantages over conventional ionic media due to their low osmolality and osmotic fluid shifts within the body are less severe". The above statement has no clinical data to substantiate this. Again, to date there are no extensive experimental data to support clear superiority of any particular contrast agent.

In European studies - A total of 46 patients were entered into the study in two-part (pilot study 16, main study 30) at one center. Iohexol was administered orally, rectally and by NG tube at concentrations ranging from 80 to 350 mgI/ml to pediatric patients with most receiving a concentration of 175 mgI/ml. The radiographic quality was optimal in all patients and no adverse events were reported.

The major concerns are diarrhea. In previous studies supporting approval of Omnipaque for examination of the gastrointestinal tract in adults, diarrhea was reported in 91% (P-633 - healthy adult male volunteers) and 76% (PS-632 - controlled study), respectively. Diarrhea was reported in 36% of subjects in the current pediatric study IOH-1058.

It is my conclusion that although iohexol is safe and effective, there is may be no clear advantage in using the higher cost, lower osmolarity iohexol over the standard agent, barium sulfate.

OVERALL CONCLUSION RELATING TO SAFETY AND EFFECTIVENESS OF OMNIPAQUE 180, 240 and 300 IN EXAMINATION OF THE GASTROINTESTINAL TRACT IN CHILDREN (Oral or RECTAL ADMINISTRATION)

Although the numbers involved are relatively small, the data clearly demonstrate the effectiveness and reasonable safety of Omnipaque 180 mgI/mL and 300 mgI/mL for use in examination of the gastrointestinal tract in pediatric patients.

The applicant has also requested approval for the use of Omnipaque 240 mgI/mL for the identical indication. Four pediatric patients were successfully studied using Omnipaque 240 in Norway. Since Omnipaque is safe and effective for this purpose at both a higher and a lower concentration, one would reasonably conclude that it is also effective at an intermediate concentration. I have no objection to the applicant's request for inclusion of Omnipaque 240 for this indication.

With regard to the concentration of iohexol providing 140 mgI/mL, the study numbers are too small (7 patients including 2 exclusions). The applicant has not requested approval for this concentration.

RECOMMENDATION

Omnipaque 180, 240 and 300 mgI/mL is recommended for approval for examination of the gastrointestinal tract in children when administered orally or rectally.

We suggest some modifications to the draft package insert.

ISI

Silas Chow, M.D.

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MEDICAL OFFICER'S REVIEW