HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
5 November 2014

IZINOVA, concentrate for oral solution

Box of 2 bottles each containing 17.510 g of sodium sulfate anhydrous, 3.276 g of magnesium sulfate heptahydrate and 3.130 g of potassium sulfate (CIP: 34009 269 952 4 9)

Applicant: IPSEN PHARMA

INN	Sodium sulfate anhydrous, magnesium sulfate heptahydrate, potassium sulfate
ATC code (2014)	A06AD10 (osmotically acting laxatives)
Reason for the request	**Inclusion**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)** **Hospital use (French Public Health Code L.5123-2)**
Indication concerned	**"IZINOVA is indicated in adults for bowel cleansing prior to any procedure requiring a clean bowel (e.g. bowel visualisation including endoscopic or radiological examination or surgical procedure)."**

Actual Benefit	**The actual benefit of IZINOVA in the Marketing Authorisation indications is substantial.**
Improvement in Actual Benefit	**IZINOVA provides no improvement in actual benefit (level V, non-existent) in bowel cleansing, compared with conventional PEG-based bowel preparations.**
Therapeutic use	**The use of IZINOVA is the same as the other products prescribed for bowel cleansing, prior to endoscopic or radiological examination, in adults, in the absence of severe renal failure or congestive heart failure and severe fluid and electrolyte imbalances.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date: 26 April 2013 (decentralised procedure, reference member state: France); Commitment within the context of the MA: post-inclusion study and final results of the phase IIIb/IV study BL1800-440
Prescribing and dispensing conditions/special status	List I

ATC Classification	2014	
	A	Alimentary tract and metabolism
	A06	Drugs for constipation
	A06A	Drugs for constipation
	A06AD	Osmotically acting laxatives
	A06AD10	Mineral salts in combination

02 BACKGROUND

This is a request for inclusion of the proprietary medicinal product IZINOVA on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use. IZINOVA is a sulfate-based saline preparation for bowel cleansing indicated prior to any procedure requiring a clean bowel.

03 THERAPEUTIC INDICATIONS

"IZINOVA is indicated in adults for bowel cleansing prior to any procedure requiring a clean bowel (e.g bowel visualisation during endoscopic or radiological examination, or surgical procedure). IZINOVA is not a treatment for constipation."

04 DOSAGE

"Dosage

Adult
Two bottles of IZINOVA are needed for appropriate cleansing of the bowel. Prior to administration, the content of each bottle must be diluted in water, using the cup provided, to a total volume of approximately 0.5 litres. For each bottle, the dose must be followed by the ingestion of an additional 1 litre of water or clear liquid within 2 hours.
Authorised clear liquids are: water, tea or coffee (no milk or cream), fizzy or still soft drinks, fruit juices without pulp (not coloured red or purple), clear soup or soup strained to remove any solids.

In total, the volume of liquid intake required for bowel cleansing is 3 litres taken orally prior to the procedure. This medicine can be taken either as a split-dose (over two days, with the first bottle taken the night before the procedure, and the second to be taken the following morning)

or as a one-day preparation as described below (see Method of Administration). The exact regimen and rate of administration of IZINOVA will be determined by the doctor.
If allowed by the timing of the procedure, the two-day, split-dose regimen should be favoured over the one-day regimen. The one-day dosing regimen may be a potentially useful alternative.

Special populations

Elderly population

No overall differences in safety or efficacy were observed between elderly patients and other patients during the clinical development of IZINOVA (see Section 5.1). Dose adjustment is not required in elderly patients. However, special precautions for use should be taken in this high-risk population (see Section 4.4).

Patients with renal impairment

Insufficient data are available for this population. Dose adjustment is not required in patients with mild to moderate renal impairment. However, special precautions should be taken in this population as for any high-risk population. IZINOVA should not be used in patients with severe renal impairment (see sections 4.3 and 4.4).

Patients with hepatic impairment

Insufficient data are available for this population. Dose adjustment is not required in patients with hepatic impairment. However, special precautions should be taken in this population as for any high-risk population.

Paediatric population

The safety and efficacy of IZINOVA in the paediatric population (patients below 18 years old) have not yet been established. No data are available (see Section 5.1)."

05 THERAPEUTIC NEED

Bowel cleansing is a procedure that involves cleaning the intestines by removing practically all faecal matter, in order to perform a diagnostic procedure (endoscopic or radiological examination) or therapeutic procedure (excision of precancerous or cancerous lesions, surgery). The aim of bowel cleansing is to allow for the best possible visualisation of the intestinal mucosa when performing these procedures. The quality of the cleansing achieved determines the quality of the examinations in terms of both sensitivity and specificity and positive and negative predictive values. Poor preparation carries an established risk of poor polyp detection. Preparation is therefore a key element in the diagnosis of bowel diseases.

There are three types of products used in France for bowel preparations for oral use, each with different modes of action.[1]

Polyethylene glycol (PEG)-based solutions, with a mechanical mode of action, are isotonic solutions that act essentially through a sweeping effect on the bowel contents. These solutions

[1] Heresbach D, Boustière C, Coffin B et al. Recommandations de la SFED. Préparation colique pour la coloscopie totale chez l'adulte. Acta endoscopica 2011;41:39-46.

do not induce fluid and electrolyte disturbances if taken correctly, i.e. in a short space of time not exceeding 3 hours. The main disadvantage of these solutions is the large volume (4 litres recommended, in reality often 3 to 3.5 litres). These solutions have an unpleasant, salty taste, although this is improved in the sulfate-free PEG preparations. Contraindications to PEG-based preparations are rare, and include renal impairment with dialysis or congestive heart failure.

Sodium phosphate-based products, with an osmotic mode of action; these laxatives require fluid replacement to prevent dehydration and fluid and electrolyte disturbances. Patients are advised to drink at least 2 litres of fluid in the 24 hours prior to the examination, which constitutes the preparation time. Sodium phosphate-based preparations are contraindicated before the age of 18 years and after 75 years or in cases of severe renal or hepatic impairment, congestive heart failure, hyperparathyroidism and inflammatory bowel disease. Precautions should be taken in patients treated with medicines that can alter glomerular haemodynamics (ACE inhibitors, ARBs, NSAIDs).

Combined sodium picosulfate and magnesium citrate solutions
Several recent studies have shown that the quality of the preparation was identical to that produced by taking PEG solutions and that it was better tolerated and accepted. The preparation comprising sodium picosulfate combined with magnesium citrate should be used after age 18 years without restriction for the elderly, but is contraindicated in cases of congestive heart failure, gastric ulcer, ascites, dehydration, rhabdomyolysis, severe renal disorders or when taking specific medications (diuretics, corticosteroids, digoxin, NSAIDs, tricyclic antidepressants or SSRIs, neuroleptics used for schizophrenia, lithium and carbamazepine).

According to the Société Française d'Endoscopie Digestive [French Society for Gastrointestinal Endoscopy], a split-dose preparation taken the day before and in the hours preceding the examination is more effective than a single dose taken the day before. Similarly, the preparation is more effective when taken within 8 hours prior to the examination.

In conclusion, the bowel preparation should meet the combined criteria of efficacy, product acceptability and safety of use, which will require adapting it to the patient's profile, ideally during a medical consultation.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Name (INN) Company	Indication	Date of opinion	AB	IAB wording	Reimbursed
BIOPEG Macrogol 4000 Potassium and sodium *Fresenius Kabi France*	This medicinal product allows for bowel cleansing in preparation for: - endoscopic examinations (allowing for visual examination of natural tubes and cavities) and radiological examinations, - bowel surgery.	Inclusion 26/09/1990	Substantial	V	Yes
COLOPEG Sodium sulfate Sodium bicarbonate Potassium chloride Sodium chloride Macrogol 3350 *Bayer*	Bowel cleansing for patient preparation prior to: - endoscopic or radiological examinations, - bowel surgery.	RI 18/11/2009	Substantial	-	Yes
FORTRANS Macrogol 4000 Sodium sulfate Sodium bicarbonate Sodium chloride Potassium chloride *Ipsen Pharma*		RI 21/11/2012	Substantial	-	Yes
KLEAN PREP Sodium sulfate Sodium bicarbonate Potassium chloride Sodium chloride Macrogol 3350 *Norgine Pharma*		RI 2/06/2010	Substantial	-	Yes

MOVIPREP Sachet A: Macrogol 3350, sodium sulfate, sodium chloride, potassium chloride Sachet B: Ascorbic acid, sodium ascorbate *Norgine Pharma*	MOVIPREP is a solution for oral administration, used for bowel cleansing prior to any examination requiring a clean bowel (e.g. endoscopic or radiological examination)	Re-assessment 9/05/2012	Substantial	MOVIPREP provides no improvement in actual benefit (IAB V) for preparation for gastrointestinal endoscopy.	Yes
CITRAFLEET Sodium picosulfate Light magnesium oxide Citric acid anhydrous *Axcan Pharma SAS*	Bowel cleansing prior to any diagnostic examination requiring a clean bowel, such as colonoscopy or radiological examination	Inclusion 30/06/2010	Substantial	In the absence of demonstrated superiority of CITRAFLEET over other bowel preparations, CITRAFLEET provides no improvement in actual benefit for the performance of gastrointestinal endoscopy (IAB V). CITRAFLEET is an additional diagnostic means.	Yes
PICOPREP Sodium picosulfate Magnesium oxide Anhydrous citric acid *Ferring SAS*	"Bowel cleansing prior to radiological or endoscopic examinations requiring a clean bowel. Bowel cleansing prior to surgery, if deemed clinically necessary."	Inclusion 15/12/2010	Substantial	PICOPREP provides no improvement in actual benefit for the performance of gastrointestinal endoscopy (IAB V) over other bowel preparations.	Yes
COLOKIT Monosodium phosphate monohydrate Anhydrous disodium phosphate *Mayoly Spindler*	"Bowel cleansing for patient preparation prior to colon surgery or prior to endoscopic or radiological examinations of the colon".	Inclusion 2/06/2010 (in the process of re-assessment)	Substantial	In the absence of proof of superiority over other bowel preparations, the proprietary medicinal product COLOKIT does not provide an improvement in actual benefit for the bowel preparation of patients with a view to endoscopy or gastrointestinal surgery (IAB V). This proprietary medicinal product is an additional diagnostic means.	Yes

FLEET PHOSPHO-SODA Disodium phosphate dodecahydrate Sodium dihydrogen phosphate dihydrate *Ferring SAS*	Bowel cleansing for patient preparation prior to colon surgery or prior to endoscopic or radiological examinations of the colon.	Re-assessment 21/05/2003 RI 15/02/2012	Substantial	Taking into account the adverse effects and the data analysed, Disodium phosphate dodecahydrate and sodium dihydrogen phosphate dihydrate provide no improvement in actual benefit (level V) over polyethylene glycol (PEG) solutions, prescribed in bowel cleansing in adults, prior to colon surgery or endoscopic or radiological examination.	Yes
PREPACOL Disodium phosphate, monosodium phosphate, bisacodyl *Guerbet*	This medicine is indicated in preparation of the colon for barium enemas or endoscopy of the colon.	-	-	-	No
X PREP Senna dry extract *Meda Pharma*	Colon preparation for barium enema or colonoscopy and before urography.	-	-	-	No

06.2 Other health technologies

Not applicable.

◗ Conclusion
The comparators mentioned are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

The proprietary medicinal product IZINOVA does not qualify for reimbursement in the countries in which it is marketed. An application for reimbursement is in progress for the Czech Republic.

COUNTRY	Marketing Authorisation	
	Date	Indications
Belgium, Czech Republic, Estonia, Germany, Greece, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Spain, United Kingdom	17 Jan. 2013	IZINOVA is indicated for adults in bowel cleansing, prior to any procedure requiring a clean colon (e.g. visualisation of the colon during endoscopic or radiological examination, or surgical procedure). IZINOVA is not a treatment for constipation.
United States	05 Aug. 2010	Preparation for bowel cleansing prior to colonoscopy in adults.

08 ANALYSIS OF AVAILABLE DATA

The request for reimbursement of the proprietary medicinal product IZINOVA is based on data from:

- two phase III non-inferiority studies, versus MOVIPREP: studies BLI800-301 and BLI800-302;
- a phase IV comparative study versus PICOPREP: study BLI800-480;
- a phase III non-inferiority study (BLI800-303), versus NULYTELY, PEG-based solution, marketed in the United States; this study proposed a different dosing regimen between the two treatment groups, considering that the dosing regimen affects the quality of the colon preparation; the efficacy data from this study were not, therefore, taken into consideration by the Committee and only the safety data will be presented in this opinion.

08.1 Efficacy

8.1.1 Phase III studies (BLI800-301 and BLI800-302)

Studies BLI800-301 and BLI800-302 are two phase III, randomised, comparative, single-blind, parallel-group, multicentre, non-inferiority studies.
The primary objective of these studies was to evaluate the efficacy and safety of IZINOVA in adult patients undergoing colonoscopy, versus MOVIPREP.

Methods
The methods of these two studies are described in Table 1. They differed in the dosing regimen of the products with a single dose for study BLI800-301 and a split dose for study BLI800-302.

Table 1. Methods of studies BLI800-301 and BLI800-302

	Study BLI800-301	Study BLI800-302
Dates and locations	11 centres in the United States July to November 2007	10 centres in the United States July to October 2007
Inclusion criteria	- Patients aged at least 18 years undergoing colonoscopy, for one of the following indications: evaluation of barium enema results, gastrointestinal haemorrhage, anaemia of unknown origin, monitoring of neoplasia, endosonography, inflammatory bowel disease, diarrhoea or constipation of unknown origin, polypectomy, laser treatment, routine monitoring - Patient in good general condition determined by physical examination and medical history.	
Primary non-inclusion criteria	- Present or suspected ileus, severe haemorrhagic rectocolitis, gastrointestinal obstruction, gastric retention, intestinal perforation, toxic colitis or megacolon - Disorders of consciousness predisposing subjects to pulmonary aspiration - Colonoscopy performed for the purpose of removing a foreign body by decompression - Clinically significant electrolyte abnormalities at the first visit - History of gastrointestinal surgery - History of renal or hepatic impairment or congestive heart failure - Phenylketonuria or G6PD deficiency.	
Treatments administered	Randomisation with a 1:1 allocation: - IZINOVA group: first dose the day before the procedure at about 6.00 p.m. (180 ml of solution diluted in water to a total of 0.5 l), followed by 1 litre of water consumed over the next hour. Second dose 1-3 hours later (same procedure) - MOVIPREP group: first dose the day before at about 6.00 p.m. (powder dissolved in 1 litre of water) in quantities of about 0.25 l every 15 minutes for 1 hour. Second dose 1 ½ hours later and drink 1 litre of additional clear liquid.	Randomisation with a 1:1 allocation: - IZINOVA group: first dose the day before the procedure at about 6.00 p.m. (180 ml of solution diluted in water to a total of 0.5 l), followed by 1 litre of water consumed over the next hour. Second dose in the morning of the procedure, 10-12 hours later (same procedure ending at least one hour before the colonoscopy) - MOVIPREP group: first dose the day before at about 6.00 p.m. (powder dissolved in 1 litre of water) in quantities of about 0.25 l every 15 minutes for 1 hour, then 0.5 l of clear liquid. Second dose in the morning, 10-12 hours later (same procedure)
Primary efficacy endpoint	Bowel cleansing success rate, using a 4-point scoring system, evaluated under single blind conditions by the investigator: -Score 1: mediocre: large quantity of residual faecal matter, further cleansing needed -Score 2: fairly good: sufficient quantity of faecal matter or fluids to prevent completely reliable examination -Score 3: good: small quantities of faecal matter or fluids that do not interfere with the examination -Score 4: excellent: only small pieces of adherent faecal matter or fluid Success was defined as bowel preparation considered “good” or “excellent” under investigator-blinded conditions (score of 3 or 4 on a four-point scale)	
Secondary endpoints	Colonoscopy status: proportion of colonoscopies completed or not	

	completed Adequacy of bowel cleansing and the need for repeat preparation	
Number of subjects needed (NSN)/ Statistical analysis	Taking into account a difference in variation of the bowel cleansing success rate of 15% between the IZINOVA group and the MOVIPREP group, the NSN was estimated at 400 to demonstrate the non-inferiority of IZINOVA (with a 15% margin; unilateral α risk = 0.025) with a 90% power.	Taking into account a difference in variation of the bowel cleansing success rate of 15% between the IZINOVA group and the MOVIPREP group, the NSN was estimated at 360 to demonstrate the non-inferiority of IZINOVA (with a 15% margin; unilateral α risk = 0.025) with a 90% power.

Results

Exposure to treatment
In study BLI800-301, 408 patients were randomised, of whom 387 received at least one dose of treatment, 194 subjects in the IZINOVA group and 193 subjects in the MOVIPREP group, representing the modified intention-to-treat population (ITTm). In the IZINOVA group, 5 patients were excluded from the per-protocol analysis due to major deviations[2] from the protocol; this number was 18 in the IZINOVA group. The percentage of patients who completed the preparation was 99% in the MOVIPREP group and 95% in the IZINOVA GROUP.

In study BLI800-302, 379 patients were randomised, of whom 364 received at least one dose of treatment, 181 subjects in the IZINOVA group and 183 subjects in the MOVIPREP group (ITTm population). Four patients in each group were excluded from the per-protocol analysis due to major deviations. The percentage of patients who completed the preparation was 98% in both treatment groups.

Patient characteristics
Patient characteristics were similar between the treatment groups in both studies. Mean patient age was 56.5 years; 24% were over 65 years and 54.5% were women.

Efficacy based on endpoints:
These two studies demonstrated the non-inferiority of IZINOVA compared with MOVIPREP in terms of bowel cleansing success rates, with upper bounds of the 95% confidence interval of less than 15% (Table 2). The per-protocol analysis confirms these results.
Of the secondary efficacy endpoints, only the adequacy of bowel cleansing was provided. The proportion of patients with adequate bowel preparation was similar in the two treatment groups and was approximately 94% in study BLI800-301 and 99% in study BLI800-302.

[2] Major deviations: deviations relating to food ingestion at dinnertime the day before or the morning of the examination, or insufficient details on food intake, and deviations relating to incomplete preparation.

Table 2. Results of the primary efficacy endpoint analysis

	Study BLI800-301 (single-dose regimen)		Study BLI800-302 (split-dose regimen)	
	IZINOVA N=194	**MOVIPREP N=193**	**IZINOVA N=181**	**MOVIPREP N=183**
Primary efficacy endpoint				
Bowel cleansing success rate, *n (%)*	159 (82.4)	155 (80.3)	175 (97.2)	175 (95.6)
Of which score 4 "excellent"	86 (44.6)	72 (37.3)	114 (63.3)	96 (52.5)
score 3 "good"	73 (37.8)	83 (43.0)	61 (33.9)	79 (43.2)
95% CI of the absolute difference between treatments	2.1 [-5.7;9.8]		1.6 [-2.2;5.4]	
p-value	0.61		0.39	

8.1.2 Phase IV study (study BLI800-480)

Study BLI800-480 is a phase IV randomised, comparative, single-blind, parallel-group, multicentre superiority study (10 centres in the United States). This study was conducted from December 2012 to April 2013.
The primary objective of this study was to evaluate the efficacy and safety of IZINOVA in adult patients undergoing colonoscopy, versus PICOPREP, using a split-dose regimen.

Methods
The patient selection criteria were very similar to those of the previous phase III studies.
Subjects were randomised in a ratio of 1:1 to receive one of the following two treatments (in a split dose over 2 days):

- IZINOVA group: first dose the evening before the procedure (180 ml of solution diluted in water to a total of 0.5 l), followed by 1 l of water consumed in the next hour. Second dose in the morning of the colonoscopy, 10-12 hours later (same procedure). The procedure had to be finished at least 3 hours before the colonoscopy.
- PICOPREP group: first dose the evening before the procedure (one sachet diluted in approximately 150 ml of water), followed by approximately 5 times 240 ml of clear liquid, consumed before bedtime. Second dose in the morning of the colonoscopy followed by at least 3 times 240 ml of clear liquid. The procedure had to be finished at least 2 hours before the colonoscopy.

The primary efficacy endpoint was the bowel cleansing success rate as defined previously.
The secondary endpoints included adequacy of bowel cleansing and the need for repeat preparation, duration of the colonoscopy and number of colonoscopies that were able to reach the caecum.
Taking into account a difference in variation of the bowel cleansing success rate of 8% between the IZINOVA group and the PICOPREP group, the number of subjects necessary was estimated at 320 to demonstrate the superiority of IZINOVA (unilateral α risk = 0.05) with an 80% power.
The primary analysis was performed on an intention-to-treat population using a Cochran Mantel Haenszel Chi-square test adjusting for the site effect.

Results
Exposure to treatment
In study BLI800-480, 368 patients were randomised, of whom 338 received at least one dose of treatment, 169 subjects in each of the IZINOVA and PICOPREP groups, representing the modified intention-to-treat population (ITTm population). In the IZINOVA group, 17 patients were excluded (per-protocol population); this number was 13 in the PICOPREP group, primarily due to withdrawal of consent.

Patient characteristics
Patient characteristics were similar between the treatment groups in both studies. Mean patient age was 58 years; 24% were 65 years or older and approximately 55% were women.

Efficacy based on endpoints:
This study demonstrated the superiority of IZINOVA over PICOPREP in terms of bowel cleansing success rates (Table 3). The per-protocol analysis confirms these results.
Of the secondary efficacy endpoints, the proportion of patients with adequate bowel preparation was in favour of IZINOVA (99% versus 95%) over PICOPREP (p=0.03), as was the number of colonoscopies able to reach the caecum (100% versus 95%; p=0.002). There was no difference between groups in the need for further preparation (1% for the IZINOVA group and 4% for the PICOPREP group; p=0.09) and the duration of colonoscopy.

Table 3. Results of the primary efficacy endpoint analysis

	Study BLI800-480 (split-dose regimen)	
	IZINOVA N=169	**PICOPREP N=169**
Bowel cleansing success rate, *n (%)*	160 (94.6)	144 (85.7)
Of which score 4 "excellent"	92 (54.4)	44 (26.2)
score 3 "good"	68 (40.2)	100 (59.5)
95% CI of the absolute difference between treatments	8.9 [2.7;15.2]	
p-value	0.006	

09 SAFETY/ADVERSE EFFECTS

9.1.1 Clinical study data

The main adverse events reported in both phase III studies are described in Table 4. The safety data of study BLI800-303 were combined with the data of the other two studies. The objective of this study was to demonstrate the non-inferiority of IZINOVA in a split dose compared with NULYTELY single dose (a PEG-based solution marketed in the United States). The study design was comparable to that of studies BLI800-301 and BLI800-302.
Two methods were used for collecting adverse events: spontaneous adverse event reporting and a gastrointestinal adverse events questionnaire. These data are combined in Table 4. The percentage of patients having at least one adverse event was comparable between treatment groups. The adverse events were predominantly gastrointestinal. As regards the one-day single-dose regimen (study BLI800-301), vomiting was more common in the IZINOVA group than in the MOVIPREP group. In study BL1800-302 (split-dose regimen), intestinal bloating and discomfort were more commonly reported in the MOVIPREP group.
No serious adverse events were reported in the IZINOVA group, compared with 4 in the MOVIPREP group, which were not related to the treatment. Two patients discontinued treatment in the IZINOVA group due to treatment-related adverse events.

Table 4. Adverse events found in clinical studies

Studies	IZINOVA		MOVIPREP		NULYTELY
	Single dose (study 301) N=194	Split dose (studies 302+303) N=244	Single dose (study 301) N=193	Split dose (study 302) N=183	Single dose (study 303) N=67
AEs, *n (%)*	**162 (83.5)**	**177 (72.5)**	**149 (77.2)**	**149 (81.4)**	**50 (74.6)**
Abdominal distension	111 (57.2)	96 (39.3)	107 (55.4)	98 (53.6)	32 (47.8)
Abdominal pain	71 (36.6)	86 (35.2)	68 (35.2)	81 (44.3)	14 (20.9)
Nausea	89 (45.9)	96 (39.3)	75 (38.9)	62 (33.9)	33 (49.3)
Vomiting	24 (12.4)	21 (8.6)	7 (3.6)	7 (3.8)	5 (7.5)
Discomfort	123 (63.4)	136 (55.7)	116 (60.1)	126 (68.9)	36 (53.7)
Headache	4 (2.1)	3 (1.2)	3 (1.6)	1 (0.5)	0

9.1.2 SPC data

The adverse effects reported during clinical trials and events observed in individual patients, according to frequency, were:

- Very common: abdominal distension, abdominal pain, nausea, vomiting, discomfort;
- Uncommon: headache, anorectal discomfort, dry mouth, dysuria, chills, increase in enzyme levels (AST, CPK, LDH), blood phosphorus increased, hyperbilirubinaemia, blood chemistry disturbances (hyponatraemia, hypokalaemia, hypocalcaemia, hyperuricaemia).
- Of indeterminate frequency: hypersensitivity (including urticaria, pruritus, rash, erythema, dyspnoea, throat tightness).

09.2 Summary & discussion

The request for inclusion of IZINOVA on reimbursement lists is based on data from 2 phase III, randomised, controlled, single-blind, multicentre, non-inferiority studies and a phase IV (post-marketing) study of the same design. A third phase III study comparing two different dosing regimens (split dose and single dose) was not taken into consideration by the Committee.

Efficacy

The objective of the two phase III studies was to evaluate the efficacy and safety of IZINOVA in adults undergoing colonoscopy, versus MOVIPREP. These studies differed in their dosing regimen:

- single-dose regimen the day before the examination for study BLI800-301
- split-dose regimen with one dose the day before and one in the morning for study BLI800-302.

These studies included 387 and 379 randomised patients respectively, all of whom received at least one dose of treatment. Mean patient age was 57 years and 55% were women.

These two studies demonstrated the non-inferiority of IZINOVA compared with MOVIPREP in terms of bowel cleansing success rates (primary efficacy endpoint), with a 95% confidence interval margin of less than 15%. The bowel cleansing success rate was evaluated under single-blind conditions by the investigator according to a 4-point score based on the quantity of residual faecal matter and the need for further bowel cleansing. In study BLI800-301, this success rate was 82.4% for IZINOVA and 80.3% for MOVIPREP. It was 97.2% and 95.6% respectively in study BLI800-302 (split-dose regimen). It should be noted that the score normally used to evaluate bowel cleansing quality is the Boston scale.

The phase IV study (study BLI800-480) was a superiority study whose objective was to evaluate the efficacy and safety of IZINOVA versus PICOPREP, using a two-day split-dose regimen. In this study 338 patients with the same characteristics as in the previous studies were randomised

and received at least one dose of treatment. This study demonstrated the superiority of IZINOVA over PICOPREP in terms of bowel preparation success rates with the following rates: 94.6% for the IZINOVA group and 85.7% for the PICOPREP group (p=0.006).

Safety
In the two phase III studies, the percentage of patients who had at least one adverse event was comparable between the two groups (72.5-83.5% in the IZINOVA group). The adverse events were predominantly gastrointestinal with abdominal distension and pain, nausea and vomiting. It should be noted that for the single-dose regimen, vomiting was more common in the IZINOVA group, whereas with the split-dose regimen, abdominal bloating and discomfort were more common in the MOVIPREP group. The same safety profile was found in the phase IV study versus PICOPREP, with no difference between the groups compared.

Comments
The score normally used to evaluate bowel cleansing quality is the Boston scale. However, the use of the four-point score chosen does not appear to be prejudicial.
However, the Committee regrets that there are no studies:

- allowing comparison of IZINOVA with the conventional PEG-based proprietary medicinal products with an appropriate methodology (administration regimen comparable between treatment groups),
- of the number of intestinal polyps detected,
- of patient satisfaction, in particular in terms of the quantity of liquid consumed.

09.3 Study programme

Within the context of the Marketing Authorisation, the company is committed to conducting several studies:

- a post-inclusion study on the real-life efficacy and safety of IZINOVA;
- study BLI800-440: a phase IIIb/IV study to evaluate the efficacy and safety of IZINOVA in adult subjects, including elderly subjects or subjects with renal or hepatic impairment;
- a paediatric efficacy and safety study in subjects aged from 12 to 17 years.

010 THERAPEUTIC USE

Bowel cleansing is necessary for the preparation of patients prior to endoscopic or radiological examination.

IZINOVA is a combination of osmotically acting laxatives (sodium sulfate, magnesium sulfate and potassium sulfate).
The use of IZINOVA is the same as the other products prescribed in bowel cleansing, prior to endoscopic or radiological examination, in adults, in the absence of severe renal impairment or congestive heart failure and severe fluid and electrolyte disturbances.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

011.1 Actual benefit

◗ Bowel cleansing is necessary for the preparation of patients prior to endoscopic or radiological examinations and colon surgery. The seriousness of the disorder is defined by the results of the examination.
◗ This proprietary medicinal product is intended to be diagnostic.
◗ The efficacy/adverse effects ratio in this indication is high.
◗ The use of IZINOVA is the same as the other products prescribed in bowel cleansing, prior to endoscopic or radiological examination, in adults, in the absence of severe renal impairment or congestive heart failure and severe fluid and electrolyte disturbances.
◗ Alternative medicinal products exist.

◗ Public health benefit:
Endoscopic or radiological examinations and surgical procedures of the colon and rectum allow for the screening, diagnosis and treatment of gastrointestinal lesions, in particular colorectal precancerous lesions or cancers (diseases which constitute a major burden).
The improvement of screening and surgical management of colorectal cancer is a public health priority (Public Health Act 2004).
In view of the clinical trial data, the proprietary medicinal product IZINOVA has not been shown to improve bowel cleansing quality compared with conventional PEG-based bowel preparations.
Therefore, the proprietary medicinal product IZINOVA is not expected to have an impact on public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of IZINOVA is substantial in the Marketing Authorisation indications.

011.2 Improvement in actual benefit (IAB)

IZINOVA provides no (level V, non-existent) improvement in actual benefit in bowel cleansing, compared with conventional PEG-based bowel preparations.

011.3 Target population

The target population of IZINOVA consists of all adult patients undergoing colonoscopy. The number of colonoscopies performed in France each year is estimated at between 1.1 and 1.2 million. This is a high estimate of the target population of IZINOVA, which is contraindicated or has not been evaluated in a certain number of patients with comorbidities (in particular renal or hepatic impairment or heart failure).
The target population is estimated at between 1.1 and 1.2 million patients per year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications and at the dosage in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

◗ Packaging

The packaging is appropriate to the prescribing conditions according to the indication, dosage and duration of treatment.