HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

30 June 2010

CITRAFLEET, powder for oral solution
B/2 - 15.08 g per dose (CIP code: 384 164-5)
B/50- 15.08 g per dose (CIP code: 572 217-5)

Applicant: AXCAN PHARMA SAS

sodium picosulphate
light magnesium oxide
anhydrous citric acid

ATC code: A06AB58

Date of Marketing Authorisation: 21 April 2008 (mutual recognition procedure, Reference Member State: UK)

Reason for the request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredients

Sodium picosulphate ……10 mg
Light magnesium oxide ……..... 3.5 g
Anhydrous citric acid ……10.97 g

1.2. Indication

"Intestinal lavage prior to any diagnostic investigation requiring a clean intestine, such as colonoscopy or radiological examination."

1.3. Dosage

"**Method of administration and dosage**
Oral administration.
A low-residue diet is recommended on the day before the examination at the hospital. In order to avoid any dehydration during treatment with CitraFleet, it is recommended to drink about 250 ml of water or other clear liquid every hour while the laxative effect persists.

Instructions for reconstitution
Reconstitute the contents of one sachet in a glass of water (approximately 150 ml). The solution obtained is cloudy in appearance. Stir for 2 to 3 minutes and then drink the solution. If it is too hot, wait until it cools down sufficiently to drink.

Adults (including the elderly) aged 18 years and older:
One sachet reconstituted in water, taken before 8am on the day before the examination. A second sachet to be taken 6-8 hours later"

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

A : Alimentary tract and metabolism
A06A : Laxatives
A06AB : Stimulant laxatives
A06AB58 : Combined preparation with sodium picosulphate

2.2. Medicinal products in the same therapeutic category

There is no other medicinal product in class A06AB58.

2.3. Medicinal products with the same therapeutic aim

Other products indicated during preparation for radiological and endoscopic examinations:

- Products based on sodium phosphates:
- FLEET PHOSPHO-SODA, oral solution
- PREPACOL, oral solution (mono- and di-sodium phosphate) and film-coated tablet (bisacodyl) (limited to colonic examinations and approved for hospital use only).

- Products based on polyethylene glycol (PEG):
- BIOPEG oral solution (approved for hospital use only)
- COLOPEG powder for oral solution
- FORTRANS powder for oral solution
- KLEAN PREP powder for oral solution

- MOVIPREP, powder for oral solution in sachets

3 ANALYSIS OF AVAILABLE DATA

The dossier submitted by the company does not present any studies conducted with CITRAFLEET. The studies presented were conducted with Picolax. The composition of Picolax is:

- sodium picosulphate 10.0 mg
- light magnesium oxide 3.5 g
- anhydrous citric acid 12.0 g

It therefore differs from CITRAFLEET with respect to the quantity of anhydrous citric acid.
Picolax is a product which is marketed in the UK, but not in France. CITRAFLEET has been considered by EMEA to be essentially similar to Picolax (UK/H/1047/01/MR).

3.1. Efficacy

The studies presented in the dossier were not conducted by the company and were obtained from a literature search. These are the same studies as in the MA dossier.

- Hughes *et al.*[1] conducted a prospective, comparative, randomised study in 102 patients aged 18 to 60 years who received either Picolax (n= 47; at the recommended dosage of 2 sachets in 2 doses) or X-Prep (n= 55; ½ bottle/day for 2 days prior to the examination), both being combined with a hydrating, low-residue diet in preparation for a double-contrast barium enema. The radiological photographs were assessed in a blinded manner by radiologists who did not know what the patients had received. The primary endpoint was the quality of preparation for the examination, scored “excellent” (2 = no faecal residues), "good" (1 =minimal faecal residues, good visibility) or "poor" (0 = faecal residues, poor visibility). A score of “excellent” or “good" was considered to be acceptable. The choice of the primary endpoint for evaluation was not specified in the publication. There was no difference between the groups in the quality of preparation for the examination (see table 1).

For the secondary endpoint “evacuation of fine particles of matter”, PICOLAX was superior to X-PREP (92% absence of fine particles vs. 52%, p<0.005).

Table 1: Comparison of the efficacy of X-Prep and Picolax

	X-PREP	Preparation judged acceptable	Picolax	Preparation judged acceptable
Number of patients	55		47	
Quality of preparation Excellent 4 3 Good 2 1	 32 (58%) 10 (18%) 6 (11%) 3 (6%)	 48 (87%)	 24 (51%) 11 (23%) 5 (11%) 3 (6%)	 40 (85%)
Poor 0	4 (7%)		4 (9%)	

1 Hughes K, et al. A new oral bowel evacuant (Picolax) for colon cleansing. Clin Radiol. 1983 ; 34:75-7.

■ Hawkins *et al.*[2] conducted a prospective, comparative, randomised study in 150 patients, who were randomised to receive either Picolax alone (PA) or Picolax preceded by a low-residue diet for 3 days (PD) or Macrogol 3350 + electrolytes (KP) (Klean-Prep).
The double-contrast barium enema photographs were evaluated in a blinded manner by radiologists.
The colon was divided into four segments:
- 1 from the caecum to the right angle,
- 2 from the transverse colon to the left angle,
- 3 the descending colon,
- 4 the sigmoid colon and rectum.

Each colon segment was scored; the percentage of patients in whom the barium enema was judged to be of a satisfactory quality was 84%, 76% and 54% in the PA, PD and KP groups, respectively.
Faecal clearance was superior in the Picolax group at the level of the descending colon; for the secondary criteria “mucus covering” and “residual fluids”, Picolax was superior to Klean-Prep.
It should be noted that the choice of the primary endpoint was not specified.

■ Dakkak et al.[3] conducted a prospective, randomised, single-blind study in patients who had to undergo colonoscopy. Prior to the examination, the patients received: Either PEG (236 g) + electrolytes [in the form of Na bicarbonate (g) + Na sulphate (23 g) + Na chloride (6 g) + K chloride (3 g)] in 4L water, or Picolax at the recommended dosage and conditions, together with a low-residue diet. The patients completed a questionnaire on the acceptability of the solutions and on the presence or absence of nausea, vomiting, abdominal pain, disturbed sleep or peri-anal pain. The time of occurrence of diarrhoea and the number of stools were also recorded.
Two experienced endoscopists assessed the quality of the preparation for the examination in a blinded manner with respect to the presence or absence of solid stools, yellowish or clear fluid, and the appearance of the wall of the caecum, of the ascending, transverse, descending and sigmoid colon, and of the rectum. Preparation was judged to be poor in cases of solid stools or yellowish liquid causing visibility to be poor in 4 out of 6 segments and was judged to be ambiguous if 3/6 segments were affected.
Fifty-nine patients were enrolled in the study: 29 in the Picolax group (20 men and 9 women, mean age 52 years [18-88] and 30 in the PEG + electrolytes group (14 men and 16 women, mean age 52 years [28-75]).
The PEG + electrolytes solution was judged to be superior to Picolax by the endoscopists on account of the overall quality of preparation (overall cleanliness of colon; $p<0.002$) and the good performance of the colonoscopy. Fourteen patients (48%) had a satisfactory intestinal lavage with sodium picosulphate and 25 (83%) with PEG + electrolytes.
The PEG + electrolytes solution resulted in a greater number of stools being evacuated (12.39 [CI95%: 9.68-15.10] vs 8.62 [CI95%: 6.93-10.30]), ($p< 0.02$).

■ Regev *et al.*[4] conducted a prospective, comparative, randomised, single-blind study in patients who had to undergo colonoscopy on an outpatient basis. The randomisation was as follows: patients with an even number ID received 2 sachets of Picolax and patients with an odd number ID received a solution of PEG + electrolytes. Before the colonoscopy, the

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2 Hawkins S, et al. Barium enema preparation: a study of low-residue diet, "Picolax' and 'Kleen-Prep'. Australia Radiol. 1996 ; 40(3):235-9.

3 Dakkak M, Aziz K, Bennett JR. Short report: comparison of two orally administered bowel preparations for colonoscopy--polyethylene glycol and sodium picosulphate. Aliment Pharmacol Ther. 1992 : 6(4):513-9.

4 Regev A, *et al.* Comparison of two bowel preparations for colonoscopy: sodium picosulphate with magnesium citrate versus sulphate-free polyethylene glycol lavage solution. Am J Gastroenterol. 1998;93

patients completed a questionnaire, which aimed to assess compliance with instructions and to determine the degree of discomfort (1 = none or slight, 2 = moderate, or 3 = severe) and the incidence of side effects of preparation for the examination. The choice of the primary endpoint was not specified in the publication.
The quality of the colonoscopies was scored in a blinded manner by one evaluator: 1 = poor (to be repeated), 2 = acceptable (with the risk of by-passing small lesions), 3 = good, or 4 = excellent.
The assessment of the quality of preparation for the examination revealed a significant difference ($p<0.05$) in the ITT population in favour of Picolax vs. PEG. In contrast, no significant difference was found in the per-protocol analysis.

- Hamilton *et al*[5] conducted a prospective, comparative, randomised study, in 69 patients aged 15 to 88 years (median age: 62 years) undergoing colonoscopy or barium enema. This was a single-blind study. Prior to the barium enema or colonoscopy, the patients completed a questionnaire, scoring pain intensity, abdominal cramps, nausea, vomiting (none, slight, moderate, severe) as well as any problems in preparing for the examination (none, difficult, very difficult) and indicating the quantity of solution ingested.
The evaluating radiologists or endoscopists scored, in a blinded manner, the quality of preparation for the examination as follows: - poor (if faecal residues impaired interpretation), - satisfactory (intermediate quality), or – excellent. There was no significant difference between the two products.
In terms of treatment compliance, there was a significant difference in favour of Picolax ($p<0.0001$) vs Klean-Prep.

3.2. Adverse effects

3.2.1. PSUR results

The PSUR (*Periodic Safety Update Report*) for CITRAFLEET covers the period from 8th June 2005 to 30th September 2009. In this period, 415,280 patients were exposed to the product and 9 adverse events were recorded. The incidence of serious adverse events was less than 1/10,000 exposed patients.

3.2.2. The SPC

The SPC states: “during clinical trials using a combination of sodium picosulphate and magnesium citrate, the most commonly reported adverse effects related to direct effects on the intestines (abdominal pain and nausea) and effects associated with the consequences of diarrhoea or dehydration (sleep problems, dry mouth, thirst, headache, fatigue)... Hyponatraemia was reported with or without associated convulsions... In epileptic patients, cases of seizures/tonic-clonic convulsions were reported, which were not accompanied by hyponatraemia.”

[5] Hamilton D, *et al.* Sodium picosulphate compared with polyethylene glycol solution for large bowel lavage: a prospective randomised trial. Br J Clin Pract. 1996 Mar;50(2):73-5.

3.2.3. The studies

In the study by Hawkins *et al.*[3], there was more nausea in the KP group (64 %) than in the PA (7 %) and PD (11 %) groups (p< 0.01). There was more abdominal pain in the KP group (64%) than in the PA (38%) and PD (35%) groups. Likewise, more patients in the KP group stated they would refuse a repeat examination with Klean-Prep (32%), while the results in the PA group were 9% and in the PD group 8%. Other adverse effects included headache, anal irritation and vomiting. There was no significant difference between the two groups, though specific values were not presented in the publication.

No significant difference was observed between the two groups with respect to incidence of nausea, abdominal pain, peri-anal pain or sleep problems. A difference was observed in the incidence of vomiting (13% in the polyethylene glycol group and 0% in the Picolax group, p<0.05) in the study by Dakkak *et al.*[4].

The main adverse effects in the study by Regev *et al.*[5] are presented in table 2. Nausea and vomiting were more common in the PEG+ electrolytes group (38% of patients) than in the Picolax group (13%) (p < 0.05).

Table 2: Main adverse effects

	Picolax (N=39) N (%)	PEG+electrolytes (N=29) N (%)
Nausea	5 (13)*	9 (31)*
Vomiting	0 (0)*	2 (7)*
Abdominal cramps	1 (3)	2 (7)
Fatigue	2 (5)	1 (3)
Palpitations	1 (3)	3 (10)
Headache	2 (5)	0 (0)
Overall incidence of adverse effects	10 (26)	12 (41)

*p<0.05

In these studies, the mean scores for discomfort and quality of preparation were compared using the Mann Whitney test. The degree of discomfort was significantly greater in the PEG+electrolytes group (mean score +/- SD: 2.3 +/- 0.7) than in the Picolax group (1.4 +/- 0.5), p<0.01.

The results of the study by Hamilton[5] on the acceptability of the treatments are presented in table 3.

Table 3: Comparison of the acceptability (for patients) of the two preparations

		None	Mild	Moderate	Severe
Pain or cramps	Picolax	18	2	2	3
	Klean-Prep	14	5	8	0
Nausea or vomiting	Picolax*	18	5	2	0
	Klean-Prep	8	14	4	1
Difficulties in finishing the preparation	Picolax*	20		5	0
	Klean-Prep	3		12	12
Proportion of preparation finished	Picolax*	24	1	1	0
	Klean-Prep	11	10	3	3

p<0.005

3.3. Conclusion

The studies presented came from the literature and were conducted with Picolax (marketed in the UK, but not in France), which has the same composition as CITRAFLEET. CITRAFLEET is therefore considered to be an essentially similar product. These study are not recent, involve small groups and none have been conducted with CITRAFLEET.
The results of these studies obtained from the literature have shown that the efficacy of Picolax, as judged with respect to the quality of the preparation, does not differ from the other comparator medicinal products, particularly those based on Macrogol (PEG) combined with electrolytes.
The adverse effects reported most frequently were gastrointestinal (nausea/vomiting, abdominal pain, meteorism, anal discomfort or pain). There appear to have been fewer adverse effects of the nausea/vomiting type with Picolax than with the comparators, particularly products based on macrogol (PEG) combined with electrolytes.

No serious adverse events occurred.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Colonic lavage is a necessary part of preparing patients prior to endoscopic or radiological investigation or colonic surgery.

The seriousness of the condition is defined by the results of the investigation.

This product is intended for diagnostic use.

The efficacy/adverse effects ratio in this indication is high.

This medicinal product is intended for first-line use.

Alternatives are available.

> Public health benefit:
> Endoscopic or radiological investigations and surgical procedures on the colon and rectum enable the detection, diagnosis and treatment of gastrointestinal lesions, particularly precancerous lesions or colorectal cancers (diseases entailing a large burden).
> Improvement of the detection and surgical management of colorectal cancer is a public health priority (Public Health Act 2004).
> In view of the data from clinical studies, CITRAFLEET has not been shown to improve the quality of intestinal lavage in comparison with the alternatives that are available in France.
> Consequently, CITRAFLEET is not expected to benefit public health in this indication.

The actual benefit of this product is substantial.

4.2. Improvement in actual benefit (IAB)

In the absence of a demonstration of superiority of CITRAFLEET over other colonic preparations, CITRAFLEET does not provide an improvement in actual benefit in the performance of gastrointestinal endoscopy (IAB V). CITRAFLEET is an additional diagnostic agent.

4.3. Therapeutic use[6]

Colonic lavage is a necessary part of preparing patients prior to endoscopic or radiological investigation.

CITRAFLEET is a combination of a laxative stimulant, sodium picosulphate, with an osmotic laxative, magnesium citrate.
The role of CITRAFLEET is the same as that of other products prescribed for colonic lavage in adults prior to an endoscopic or radiological examination.
In patients with severe renal impairment, another preparation should be used due to the risk of magnesium accumulating in the plasma.

4.4. Target population

It is estimated that 1.1 to 1.2 million colonoscopies are performed each year in France, with a quarter of these involving polypectomy[7]. This range of 1.1 to 1.2 million could be a high estimation of the target population for CITRAFLEET. In fact, CITRAFLEET is contraindicated in a certain number of patients with comorbidities (such as congestive heart failure, hypermagnesaemia, toxic megacolon).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the marketing authorisation.

4.5.1. Packaging: appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 65 %

[6] ANAES Recommendations April 2004 : Lower gastrointestinal endoscopy: indications outside population screening

[7] Canard JM, Acta endoscopica, 2007, Letter from SFED, 2 days of endoscopy in France, survey results 2006