

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as amended**

**Dulcolax
Prepacol
Fenolax
(Bisacodyl)**

DK/W/002/pdWS/001

Rapporteur:	DK
Start of the procedure (day 0):	04-02-2009
Date of this report:	04-12-2009
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Date re-start procedure (day 90):	21-10-2009
Deadline for CMS's comments (day 115):	15-11-2009
Finalisation procedure (day 120):	20-11-2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	<ol style="list-style-type: none"> 1. Dulcolax 2. Prepacol 3. Fenolax
INN (or common name) of the active substance(s):	Bisacodyl
MAH (s):	<ol style="list-style-type: none"> 1. Boehringer Ingelheim 2. Guerbet 3. ICN Polfa Rzeszow
Pharmaco-therapeutic group (ATC Code):	A06AB02
Pharmaceutical form(s) and strength(s):	<i>Boehringer Ingelheim</i> Coated tablets 5 mg Suppositories 5, 10 mg <i>Guerbet</i> Coated tablets 5 mg (with a fluid phosphate laxative) <i>ICN Polfa Rzeszow</i> Dragees 5 mg
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I. EXECUTIVE SUMMARY

There are approved paediatric posologies for the indication of bisacodyl in children and adolescents; however these posologies vary between MAHs. The indications and recommended doses are largely based on expert opinion and clinical experience (bisacodyl has been used for more than 50 years as a laxative agent in children and adults), although some experimental studies, albeit often with an inferior methodology, have demonstrated efficacy, particularly for the use of bisacodyl as a bowel cleansing agent in children.

The data packages submitted by the MAHs under article 45 of the Paediatric Regulation comprises both company sponsored expert reports and clinical non-sponsored studies. Among these there are no prospective randomized studies of the effect on relieving constipation in the paediatric age group. Many of the submitted studies (including a few randomized studies) are manometer studies, which show that bisacodyl can stimulate the occurrence of high-amplitude-propagating contractions (HAPCs) that are thought to represent mass movement of colon contents. Also, a few randomized studies demonstrate bisacodyl to be an effective bowel cleansing agent. The dosages have varied between 5 mg per day and 15 mg per day for oral bisacodyl and between 5 mg per day and 10 mg per day for bisacodyl suppositories (often administered on a weight basis), and the examined age groups have ranged between 8 months and 17 years, however with only few studies focused on age groups below 2 years.

Two MAHs also have summarised the adverse events which have been received by the companies relating to use in children. Bisacodyl have been found to be safe in adults as well as in children.

Certain changes in to the European SmPC texts have been proposed by one MAH based on the data presented.

II. RECOMMENDATION

Based on the review of the presented paediatric data on safety and efficacy, the rapporteur considers that the benefit risk ratio is in favour to maintain an indication for oral and rectal bisacodyl in the paediatric age group:

The presented data support a variation application for the use of bisacodyl in the paediatric population with constipation.

For consistency between bisacodyl containing products across the EU, it is recommended that the SmPC contains the following:

For orally and rectally administered bisacodyl

4.2 Posology and administration

Children aged 10 years or younger with chronic constipation should only be treated under the guidance of a physician. Bisacodyl should not be used in children below 2 years of age.

Short-term treatment for constipation:

Adults and children over 10 years:

1 - 2 coated tablets (5 - 10 mg) daily before bedtime, or
1 suppository (10 mg) for immediate effect.

Children 2 - 10 years: 1 coated tablet (5 mg) daily before bedtime, or
1 suppository (5 mg) for immediate effect.

For preparation of diagnostic procedures and preoperatively

Should only be used under medical supervision.

Adults and children over 10 years

2 coated tablets (10 mg) in the morning and 2 coated tablets (10 mg) in the evening and 1 suppository (10 mg) on the following morning is recommended.

Children 4-10 years of age: 1 coated tablet (5 mg) in the evening and one suppository (5 mg) on the following morning is recommended.

Due to the specific pharmaceutical form of the product from Guerbet (bottle containing a phosphate laxative and 4 (5 mg each) film-coated bisacodyl tablets for use as bowel preparation specifically for adults, the present posology should be maintained (*For adults only. Do not administer to children below the age of 15 years*).

III. INTRODUCTION

On 3 November 2008, the MAH (Boehringer Ingelheim), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted 4 in-house reports for bisacodyl where Boehringer Ingelheim was the sponsor. Further, the MAH has submitted copies of 15 published experimental studies of bisacodyl in the paediatric age group.

A short critical expert clinical overview has also been provided. The MAH proposes the following added to the present posology in children and adolescents in the SPC, section 4.2:

Children aged ≤ 10 years with chronic or persistent constipation should only be treated under the guidance of a paediatric specialist.

When children respond to DULCOLAX with abdominal pains and/or diarrhea, daily dosing should be reduced to one tablet or one paediatric suppository given 2-3 times weekly.

The MAH has submitted their CCDS from which the following posology can be derived:

For constipation

Adults and children over 10 years: 1 - 2 coated tablets (5-10 mg), or
1 suppository (10 mg)

Children 4-10 years: 1 coated tablet (5 mg), or
1 paediatric suppository (5 mg)

Children under 4 years: 1 paediatric suppository (5 mg)

For preparation of diagnostic procedures and preoperatively

Should only be used under medical supervision.

Children 4 years of age and over: 1 coated tablet (5 mg) in the evening and one paediatric suppository (1 mg) on the following morning is recommended.

On 29 October 2008, the MAH (Guerbet), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted copies of 10 studies of the use of bisacodyl.

A clinical expert statement been provided. The MAH finds no grounds for updating the SPC. The present posology in children and adolescents for bisacodyl in the SPC reads:

4.2 Posology and administration

For adults only. Do not administer to children under the age of 15 years.

4.4 Special warnings and special precautions for use

Special warnings

In the absence of clinical trials in children and in view of the potential toxicity of the oral laxative solution in children, this medicine must only be used in adults.

On 30 October 2008, the MAH (ICN Polfa Rzeszow), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use submitted 2 in-house reports for bisacodyl where the MAH was the sponsor. The MAH does give information on other published studies of bisacodyl in the paediatric age group, however only as short abstracts in connection with the PSUR.

A short critical expert clinical overview has also been provided. The MAH finds no grounds for updating the SPC.

The present posology in children and adolescents for bisacodyl in the SPC reads:

4.2 Administration and the way of application

Adults and children over 10: orally, from 5 mg to 10 mg (from 1 to 2 tablets), once a day (usually before going to bed).

Children at the age between 4 and 10: orally, 5 mg (1 tablet) once a day (usually before going to bed).

Children under 4: the preparation is not recommended in this age group.

Rapporteur's comment

The MAHs have not provided information regarding the methods used for review of the literature. One MAH has not submitted a critical expert clinical review, and 1 MAH has not submitted an SPC.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Many studies do not specify which kind of oral or rectal bisacodyl-containing formulation that has been used.

In the MAH in-house studies the following pharmaceutical formulations have been used:

U65-0193. A clinical expert report on the paediatric use of La96a in the form of sugar-coated tablets 5 mg.

Bisacodyl, 5 mg tablets.

U68-0202. Preliminary report on a clinical trial investigating the use of La 96a in barium enema examination of the colon.

Bisacodyl, 10 mg dissolved in 2 ml propylene glycol.

U70-0375. A clinical trial of the product LA 96 A (Dulcolax) Suppositories.

Bisacodyl, 5 mg suppositories.

U73-0284. Report on the clinical trial with the preparation Dulcolax Micro-enema.

Bisacodyl enema, 10 mg.

Clinical assessment of Bisacodyl of Polfa for oral administration.

Bisacodyl, 5 mg tablets.

Usefulness of Bisacodyl dragees for preparation of patients for radiographic procedures.

Bisacodyl, 5 mg tablets.

IV.2 Non-clinical aspects

No studies have been submitted.

IV.3 Clinical aspects

IV.3.1. Introduction

Boehringer Ingelheim

The MAH has submitted 4 efficacy and safety expert reports where the MAH or partner was the sponsor:

- 1. U65-0193. A clinical expert report on the paediatric use of La96a in the form of sugar-coated tablets 5 mg.**
- 2. U68-0202. Preliminary report on a clinical trial investigating the use of La 96a in barium enema examination of the colon.**
- 3. U70-0375. A clinical trial of the product LA 96 A (Dulcolax) Suppositories.**
- 4. U73-0284. Report on the clinical trial with the preparation Dulcolax Micro-enema.**

Copies of 15 experimental studies has been submitted:

1. **van den Berg MM et al. Colonic manometry as predictor of cecostomy success in children with defecation disorders. J Pediatr Dis 2006;41:730.**
2. **Shaoul R, Haloon L. An assessment of bisacodyl-based bowel preparation for colonoscopy in children. J Gastroenterol 2007;42:26.**
3. **Godbole PP et al. Idiopathic megarectum in children. Eur J Pediatr Surg 2001;11:48.**
4. **DiLorenzo C et al. Bisacodyl but not edrophonium stimulates high amplitude propagated colon contractions (HAPCs) in children. Gastroenterology 104.**
5. **Pinfield A, Stringer MD. Randomised trial of two pharmacological methods of bowel preparation for day case colonoscopy. Arch Dis Child 1999;80:181.**
6. **Stringer MD et al. A prospective audit of paediatric colonoscopy under general anaesthesia. Acta Paediatr 1999;88:199.**
7. **Hamid SA et al. Bisacodyl and high-amplitude-propagating colonic contractions in children. J Pediatr Gastroenterol Nutr 1998;27:398.**
8. **Keuzenkamp-Jansen CW et al. Diagnostic dilemmas and results of treatment for chronic constipation. Arch Dis Child 1996;75:36.**
9. **Abubakar K et al. Preparing the bowel for colonoscopy. Arch Dis Child 1995;73:459.**
10. **Forsythe WI, Kinley JG. Bowel control of children with spina bifida. Develop Med Child Neurol 1979;12:27.**
11. **Coelho WD et al. Preparo reto-colico pelo diacetoxi-difenil-piridil-pentano para exams proctologicos em criancas. Folha Med 1967;55:399.**
12. **Aue H. Klinische Erfahrungen mit einem Kontaktlaxativum bei Kindern und Jugendlichen. Die Medizinische 1955;3:118.**
13. **Portorreal A and Kawakami E. Intestinal preparation for colonoscopy with oral bisacodyl and phosphate enema in children and adolescents. GED 2001;20:11.**
14. **El-Baba MF et al. A prospective study comparing oral sodium phosphate solution to a bowel cleansing preparation with nutrition food package in children. J Pediatr Gastroenterol Nutr 2006;42:174.**
15. **Pharmakokinetik und laxierende Wirkung von Bisacodyl nach Gabe verschiedener Zubereitungsform. Arzneim.-Forsch./Drug Res 1988;38:570.**

Finally, 11 reviews/medical position papers have been submitted. No systematic reviews are enclosed.

Guerbet

The MAH has not submitted any sponsored reports or studies.

Copies of the following 10 experimental studies were submitted:

1. **Abubakar K et al. Preparing the bowel for colonoscopy. Arch Dis Child 1995;73:459.**
2. **Bassotti G et al. Endoluminal instillation of bisacodyl in patients with severe (slow transit type) constipation is useful to test residual colonic propulsive activity. Digestion 1999;60:69.**
3. **El-Baba MF et al. A prospective study comparing oral sodium phosphate solution to a bowel cleansing preparation with nutrition food package in children. J Pediatr Gastroenterol Nutr 2006;42:174.**
4. **Godbole PP et al. Idiopathic megarectum in children. Eur J Pediatr Surg 2001;11:48.**
5. **Hamid SA et al. Bisacodyl and high-amplitude-propagating colonic contractions in children. J Pediatr Gastroenterol Nutr 1998;27:398.**
6. **Kiely EM et al. Antegrade continence enemas in the management of intractable faecal incontinence. J R Soc Med 1995;88:103P.**
7. **Pinfield A, Stringer MD. Randomised trial of two pharmacological methods of bowel preparation for day case colonoscopy. Arch Dis Child 1999;80:181.**
8. **Portorreal A, Kawakami E. Intestinal preparation for colonoscopy with oral bisacodyl and phosphate enema in children and adolescents. GED 2001;20:11.**
9. **Shaoul R, Haloon L. An assessment of bisacodyl-based bowel preparation for colonoscopy in children. J Gastroenterol 2007;42:26.**
10. **van den Berg MM et al. Colonic manometry as predictor of cecostomy success in children with defecation disorders. J Pediatr Dis 2006;41:730.**

ICN Polfa Rzeszow

The MAH has submitted 2 in-house reports:

1. **Clinical assessment of Bisacodyl of Polfa for oral administration.**
2. **Usefulness of Bisacodyl dragees for preparation of patients for radiographic procedures.**

IV.3.2. Clinical study(ies)

Bisacodyl

Bisacodyl is a diphenylmethane derivative that was first used as a laxative in 1953 due to its similarity to phenolphthalein. It is hydrolysed in the intestinal mucosa to the active compound bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM).

Bisacodyl is used in the following indications:

- Via the oral route or rectal route for the short-term (days) treatment of constipation.
- Via the oral and rectal route for bowel preparation prior to abdominal X-ray examinations, surgery and colorectal endoscopic examinations.

Bisacodyl has its effects locally in the large intestine. It stimulates sensory nerve endings resulting in increased peristaltic colonic contractions and increases its laxative effect by also inhibiting intestinal water and electrolyte absorption. It stimulates defaecation about 6 hours after oral administration and after 30-60 minutes after rectal administration.

Constipation in children

Constipation describes the infrequent passage of hard stools, often with involuntary loss of faeces in the underwear (encopresis). Constipation occurs commonly in children; however figures for prevalence and incidence of constipation in children vary widely, depending on its definition. The majority of children with constipation have so-called functional constipation, i.e. they do not have a medical disease or disorder causing the constipation. Functional constipation is associated with painful bowel movements and resultant withholding of faeces by the child. After several days without a bowel movement, irritability, abdominal distension, cramps and a decreased oral intake may result.

Rarely, a disorder causes infants and children to have significant problems moving their bowels. Foremost among these is Hirschsprung's disease, a rare congenital condition, in which a segment of the colon lacks ganglion cells. Other conditions which can lead to chronic constipation are, e.g. cystic fibrosis, cerebral palsy or spinal cord problems.

Boehringer Ingelheim

Sponsored reports and studies

- 1. Expert report U65-0193. A clinical expert report on the paediatric use of La96a in the form of sugar-coated tablets 5 mg.**

Description

This study is an expert report describing the effect and tolerability of children treated with oral bisacodyl for recurrent constipation. Results are not computed.

Methods

Objective(s):

To describe the effect and tolerability in children of oral bisacodyl.

Study design:

Open label uncontrolled single centre study.

Study population /Sample size:

Children aged 8 months to 14 years with complaints of chronic recurrent constipation, treated as out- or in-patients, and with several accompanying illnesses.

Treatments:

The initial doses varied, depending on age of child, the severity of constipation and the response obtained – between 5 mg bisacodyl per day for 2-10 days and 10-15 mg for 2-5 days. With normalization of bowel movement, dose administration was adjusted with the most common dose being 5 mg every other day.

Number of Patients (Total and for each centre):

Forty-seven children.

Outcomes/endpoints:

Only rated qualitatively by the author. Some children had routine blood tests performed.

Statistical Methods:

None performed.

Results**Recruitment/ Number analysed:**

Forty-seven children

Baseline data:

None presented.

Pharmacokinetic results:

None presented.

Efficacy results:

The treatment was described as effective in 45 out of 47 children.

Safety results:

No changes in blood tests were encountered. A tendency of diarrhoea was present that required reduction of dose.

Discussion

An expert report with data from 47 individual cases treated with oral bisacodyl for recurrent constipation apparently with good effect and tolerability.

Rapporteur's comments

An open study with an inadequate description of methodology and with no computed results. The study carries little weight to argue for clinical efficacy and safety of bisacodyl in the paediatric patient.

2. Expert report U68-0202. Preliminary report on a clinical trial investigating the use of La 96a in barium enema examination of the colon.

A preliminary report of 100 barium enema examinations. Ages were 9 to 89 years, with age group 40-60 years most heavily represented. Different methods and solutions were used to empty the colon. Contrast enemas containing 10 mg bisacodyl dissolved in 2 ml propylene glycol were administered.

Discussion

No specifics in children are presented.

Rapporteur's comments

The expert report cannot be used to assess the benefit of bisacodyl in barium enema examination in children.

3. U70-0375. A clinical trial of the product LA 96 A (Dulcolax) Suppositories

Description

This study is an expert report describing the effect and tolerability of children treated with rectal bisacodyl for recurrent constipation. Results are not computed.

Methods

Objective(s):

To describe the effect and tolerability in children of rectal bisacodyl.

Study design:

Open label uncontrolled single centre study.

Study population /Sample size:

Children aged 18 months to 14 years with complaints of chronic constipation of any cause and children who were being prepared for radiographic examination (n = 7).

Treatments:

Suppositories (5 mg bisacodyl per suppository) were prescribed for varying periods; some children receiving continuous treatment with daily administration from 2 days to 2 weeks, other children longer treatment were prescribed intermittently. Usually 1 suppository daily was administered regardless of age.

Number of Patients (Total and for each centre):

Forty children.

Outcomes/endpoints:

The time of onset of effect of the product, the nature of stools before and after treatment, the lasting nature, or otherwise, of the changes obtained. Tolerability was examined and some children had routine blood tests performed.

Statistical Methods:

None performed.

Results

Recruitment/ Number analysed:

Forty children.

Baseline data:

None presented.

Pharmacokinetic results:

None presented.

Efficacy results:

Only clinical case histories are presented. In 38 out of 40 children, a stool was passed after each suppository within periods ranging from 10 to 80 minutes, with an average of 30 minutes. In 37 out of 40 children the evacuated stool was of a normal consistency, appearance and volume.

Safety results:

Tolerability was excellent and no changes in blood tests were observed (n = 10).

Discussion

An expert report with data from 40 individual cases treated with bisacodyl suppositories for constipation and for preparation of radiologic examination apparently with good effect and tolerability.

Rapporteur's comments

An open study with an inadequate description of methodology and with no computed results. The study carries little weight to argue for clinical efficacy and safety of rectal bisacodyl in the paediatric patient.

4. U73-0284. Report on the clinical trial with the preparation Dulcolax Micro-enema.

Description

This study is an expert report describing the effect and tolerability of children treated with rectal bisacodyl for constipation. Results are not computed.

Methods

Objective(s):

To describe the effect and tolerability of children treated with rectal bisacodyl for constipation.

Study design:

Open label uncontrolled single centre study.

Study population /Sample size:

Children aged 7 months to 12 years with complaints of constipation of any cause.

Treatments:

1 microenema containing 10 mg of bisacodyl per day.

Number of Patients (Total and for each centre):

Forty children.

Outcomes/endpoints:

The latency time for laxative effect; presence of any other evacuations, stool consistency; occurrence of side effects.

Statistical Methods:

None performed.

Results**Recruitment/ Number analysed:**

Forty children.

Baseline data:

None presented.

Pharmacokinetic results:

None presented.

Efficacy results:

The results are described as on the whole very satisfactory. Particularly in the smaller children, the onset of laxative effect was rapid (most within half an hour).

Safety results:

Tolerability was good in 3 cases and excellent in all the other children.

Discussion

An expert report with data from 40 individual children treated with bisacodyl enema for constipation.

Rapporteur's comments

An open study with an inadequate description of methodology and with no computed results. The study carries only little weight to argue for clinical efficacy and safety of rectal bisacodyl in the paediatric patient.

Published experimental studies

1. van den Berg MM et al. Colonic manometry as predictor of cecostomy success in children with defecation disorders. *J Pediatr Dis* 2006;41:730.

Description**Methods****Objective(s):**

To evaluate the predictive value of colonic manometry on the clinical outcome of cecostomy in children with defecation disorders.

Study design:

Restrospective study based on medical report information.

Study population /Sample size:

Children with defecation disorders such as idiopathic constipation, Hirschsprung disease, cerebral palsy, imperforate anus, and spinal abnormality who underwent placement of a cecostomy for administration of antegrade enemas and who had colonic manometry before the procedure.

Treatments:

Colonic manometry was performed according to standard procedures: 1 hour of fasting and 1 hour after administration of a meal, and 20 minutes after bisacodyl infusion, 0.2 mg/kg, max 10 mg, through the manometry catheter.

Outcomes/endpoints:

Clinical success defined as normal defecation frequency (5 per week to 3 per day) with no or occasional faecal incontinence.

Statistical Methods:

The predictive value of colonic manometry findings and response to bisacodyl on the probability of clinical success were evaluated by binary logistic regression models and Fisher's exact test.

Results**Recruitment/ Number analysed:**

Thirty-two children, age range 2-17 years.

Baseline data:

Not relevant.

Pharmacokinetic results:

None presented

Efficacy results:

A colonic response with HAPC after bisacodyl administration was predictive of clinical success ($P = 0.03$). Absence of HAPC in the colon was significantly associated with unsuccessful outcome.

Safety results:

None presented.

Discussion

This restrospective study shows that the occurrence of HAPC after bisacodyl infusion into the colon is predictive of clinical success of cecostomy in children with defaecation disorders.

2. Shaoul R, Haloon L. An assessment of bisacodyl-based bowel preparation for colonoscopy in children. *J Gastroenterol* 2007;42:26.

Description

This study compares the effect of bisacodyl on bowel preparation for colonoscopy in a population of children with a historical population of children who had been prepared with a polyethylene glycol-electrolyte solution and sodium phosphate.

Methods

Objective(s):

To study the effectiveness of bisacodyl and a fleet enema together with a half day of a clear fluid diet.

Study design:

Children were included prospectively and compared with historical controls.

Study population /Sample size:

Children who were referred for a colonoscopy.

Treatments:

After a regular breakfast on the day prior to colonoscopy, the child received 5 mg bisacodyl orally and started a clear fluid diet. An additional bisacodyl tablet of 5 mg was taken in the evening before colonoscopy by children older than 5 years. A fleet enema, containing 16 g of biphosphonate and 6 g of sodium phosphate per 100 ml at a dose of 6 ml/kg was performed on the evening prior the procedure and repeated on the morning of the procedure. The children were compared with children who had been prepared with a polyethylene glycol-electrolyte solution and sodium phosphate.

Outcomes/endpoints:

The adequacy of bowel preparation was classified as grade 1 if no faecal material was encountered, grade 2 if small amounts of faecal material were present in scattered locations, and grade 3 for a poor preparation with faecal material precluding the visualisation of the bowel mucosa. Compliance was evaluated as fully compliant, partially compliant or non-compliant.

Statistical Methods:

None described

Results

Recruitment/ Number analysed:

98 children with a mean age of 8.7 years (range 30 months to 12 years) were compared with 26 historical children with a mean age of 6.5 years.

Baseline data:

The bisacodyl group was 2 years older than the control group ($P = 0.002$). The indications for colonoscopy, success of colonoscopy and the findings were equally distributed between groups.

Pharmacokinetic results:

None presented.

Efficacy results:

The results of the bowel preparation with bisacodyl were good to excellent in 95 % of patients and 5 % had a poor bowel preparation. The bisacodyl group had better bowel preparation than the control group; however the differences were not significant. The compliance of the bisacodyl group was 100 % compared with that of the control group (88 %).

Safety results:

No adverse events were reported in the bisacodyl group.

Discussion

The results of this study show that bisacodyl and a fleet enema is effective in bowel preparation before colonoscopy. This is an open study with historical controls and thus with insufficient methodology, which makes the interpretation of the results dubious.

3. Godbole PP et al. Idiopathic megarectum in children. Eur J Pediatr Surg 2001;11:48.

A retrospective descriptive study of 29 children (median age 8 years; range 3.5-14 years) with idiopathic megarectum with severe constipation and soiling. Three children had had surgery. Fifteen were treated by a single manual evacuation and rectal washout followed by bisacodyl, 5-10 mg daily. After a median follow-up of 16 months, 13 continued to respond well (one daily bowel action, no soiling), and 2 children remained symptomatic. The remaining 11 children had continued conventional treatment with oral laxatives, however with minor success (only 4 improved).

Discussion

This is a retrospective study of the outcome after months' to years' treatment with bisacodyl suppositories for severe constipation in children. Non-randomisation makes it difficult to evaluate the effect of bisacodyl.

4. DiLorenzo C et al. Bisacodyl but not edrophonium stimulates high amplitude propagated colon contractions (HAPCs) in children. Gastroenterology 1993;104:A498.

40 children, age 1-17 years, were randomized to receive either topical bisacodyl (0.2 mg/kg infused through a manometry catheter into the transverse colon or edrophonium (0.1 mg/kg i.v.) during a colon manometry study. Children suffered from intestinal pseudoobstruction (n = 26), functional fecal retention (n = 9) and non-ulcer dyspepsia (n = 5). Bisacodyl induced HAPCs in all the 14 children who had HAPCs after feeding and in 1 out of 6 who did not. Edrophonium induced HAPCs in 3 of 11 who had HAPCs after feeding and in none of those who did not. Speed of propagation and amplitude of bisacodyl-induced HAPCs were similar to spontaneous HAPCs.

Discussion

The study suggests that bisacodyl can induce high-amplitude propagated colon contractions in children. The study is presented in abstract form only.

5. Pinfield A, Stringer MD. Randomised trial of two pharmacological methods of bowel preparation for day case colonoscopy. Arch Dis Child 1999;80:181.

Description

Single blind randomised study comparing the efficacy of two bowel cleansing regimens prior to colonoscopy, one of which included bisacodyl.

Methods

Objective(s):

To compare the efficacy and tolerance of oral bisacodyl in combination with unrestricted diet and a phosphate enema with a standard outpatient bowel preparation method of oral picosulphate and clear fluids.

Study design:

Prospective single blind randomised study.

Study population /Sample size:

Children aged between 18 months and 16 years referred for daytime colonoscopy. Seventy children were eligible, 66 were invited to participate. No power calculations were made.

Treatments:

Picosulphate (Picolax) was given as two oral doses 24 and 18 hours before colonoscopy, allowing no solid foods but a liberal intake of clear fluids. Picolax dosages were depending of age and weight. For the 1-5 years old 5 mg bisacodyl, and for children over 5 years old 10 mg bisacodyl was given each morning for 2 days before endoscopy in combination with a phosphate enema on the morning of colonoscopy. In the bisacodyl-group an unrestricted diet up until 6 hours before colonoscopy and clear fluids until 3 hours before was allowed.

Outcomes/endpoints:

The adequacy of bowel preparation graded as: grade 1, poor preparation; grade 2, good preparation, small amounts of faecal material in scattered locations; grade 3, excellent preparation, no faecal material.

Statistical Methods:

Chi square test.

Results

Recruitment/ Number analysed:

Of the 66 children who accepted to participate, 63 completed the trial (3 cancelled and rescheduled their colonoscopy for reasons unrelated to the bowel preparation). Thirty-one patients were randomised to the bisacodyl group and 32 to the Picolax group.

Baseline data:

Age and weight were equally distributed. Colonoscopic diagnoses were similarly distributed in the two groups.

Pharmacokinetic results:

None presented.

Efficacy results:

Bowel cleansing (and compliance with medication) after bisacodyl were graded significantly worse compared to cleansing after Picolax ($P < 0.01$). The bowel preparation was good or excellent in 22 of 31 children on bisacodyl whereas in the Picolax group all children had good or excellent bowel preparation.

Safety results:

Six children in the bisacodyl group experienced abdominal pain.

Discussion

Well-conducted single blind randomised study comparing two bowel cleansing regimens prior to colonoscopy, one of which included bisacodyl, the other Perilax. Although cleansing with Perilax proved to be better than with bisacodyl, 2 out of 3 still demonstrated good or excellent cleansing with bisacodyl. However, due to an administrative error, 14 of 28 patients older than 5 years in the bisacodyl group received only half of the scheduled phosphate enema dose which might have influenced the results.

6. Stringer MD et al. A prospective audit of paediatric colonoscopy under general anaesthesia. Acta Paediatr 1999;88:199.

A prospective audit of current practice of paediatric colonoscopy from a UK department. Bowel preparation was with Picolax, or with bisacodyl in combination with a phosphate enema. Thirteen colonoscopies were incomplete due to inadequate bowel preparation or due to difficulties to pass a flexure.

Discussion

The study does not address bisacodyl efficiency for bowel preparation.

7. Hamid SA et al. Bisacodyl and high-amplitude-propagating colonic contractions in children. J Pediatr Gastroenterol Nutr 1998;27:398.

Description

A manometry study to examine the response on high-amplitude-propagating contractions of intracolonic bisacodyl administration.

Methods

Objective(s):

The aim of the study was to find a provocative agent that could be used to shorten colonic manometry testing time for children who cannot eat.

Study design:

First part of the study was a randomized open study.

Study population /Sample size:

The study is divided in 4 parts:

1 part: Comparison between bisacodyl and edrophonium: 40 children were studied, aged 1-17 years (mean 6.5 years) with pseudoobstruction (n = 26); functional faecal retention (n = 9); and unspecified functional bowel disorder (n = 5).

2 part: Comparison of spontaneous and bisacodyl-induced contractions: 7 children with functional faecal retention were studied (mean age 6.7 years).

3 part: Comparison of the response to intracecal and intrarectal bisacodyl: 7 children with functional faecal retention were compared with 6 patients with the same diagnosis who were tested with intracecal bisacodyl.

4 part: To determine whether the response to bisacodyl predicted spontaneous high-amplitude-propagating contractions (HAPCs) during colonic manometry. Twenty-eight children with functional faecal retention were compared with those in 9 children with pseudo-obstruction.

Treatments:

1 part: 0.2 mg/kg bisacodyl suspended in 5 ml of water through a colonic manometry catheter instilled in the cecum or 0.1 mg/kg intravenous edrophonium.

2 part: 0.2 mg/kg bisacodyl infused in the cecum.

3 part: Study the time until first bisacodyl-induced HAPCs after cecal administration For rectal instillation a suppository cut to size to provide bisacodyl 0.2 mg/kg.

Outcomes/endpoints:

Pressure recording (duration and velocity of HAPCs) in the large intestine, from the cecum to the rectum at fasting, one hour after a meal and 30 min after administration of a provocative agent.

Statistical Methods:

Unpaired t-test and Fishers exact test.

Results**Recruitment/ Number analysed:**

Described above

Baseline data:

Data not presented.

Pharmacokinetic results:

None presented.

Efficacy results:

1 part: Bisacodyl induced HAPCs in all 14 children who had spontaneous HAPCs and in 1 of 6 children who did not, while edrophonium induced HAPCs in 3 out of 11 children who had spontaneous HAPCs and in none of the 9 who did not have spontaneous HAPCs ($P < 0.001$).

2 part: Amplitude, duration propagation velocity, and sites of origin and extinction of spontaneous and bisacodyl-induced HAPCs did not differ.

3 part: The effect of intrarectal bisacodyl was similar to that of intracecal bisacodyl except for a delay of 10 minutes in onset.

4 part: Bisacodyl induced HAPCs in all 28 children without evidence of neuromuscular disease and 2 of 9 children with a colonic neuromuscular disease and no spontaneous HAPCS.

Safety results:

None reported

Discussion

The results of this open study suggest that bisacodyl-induced HAPCs are quantitatively and qualitatively similar to naturally occurring HAPCs, and that bisacodyl can induce HAPCs foremost in children with functional faecal retention.

8. Keuzenkamp-Jansen CW et al. Diagnostic dilemmas and results of treatment for chronic constipation. Arch Dis Child 1996;75:36.

A retrospective study with the aim to identify the presenting symptoms of chronic functional constipation in children 0-18 years of age referred to a paediatric department. One-hundred-and-eighty-three of the children were treated with bisacodyl at a dose of 0.35 (0.16) mg/day, taken for approximately 8 weeks.

Discussion

This retrospective study does not contain information on the effect or safety of bisacodyl.

9. Abubakar K et al. Preparing the bowel for colonoscopy. Arch Dis Child 1995;73:459.**Description**

An open study examining the efficacy of 2 days bisacodyl treatment in combination with a phosphate enema in preparing children for a colonoscopy.

Methods**Objective(s):**

The aim of the study was to determine the efficacy of oral bisacodyl combined with a single phosphate enema as a bowel preparation regimen in children.

Study design:

Open prospective trial.

Study population /Sample size:

Thirty children.

Treatments:

The children were given oral bisacodyl on each morning of the two days before colonoscopy. A phosphate enema was administered on the morning of the procedure. Children 5 years and older were given 10 mg bisacodyl daily and 128 ml of phosphate enema. Children less than 5 years were given 5 mg each morning and 64 ml of phosphate enema. There were no restrictions on the children's diet.

Outcomes/endpoints:

The adequacy of bowel preparation graded as grade I if no faecal material was encountered, grade II if small amounts of faecal material were present in scattered locations, and grade III if there was poor preparation with faecal material precluding satisfactory visualisation of the bowel mucosa. Also, number of stools passed when taking bisacodyl, abdominal pain, vomiting and faecal soiling were registered.

Statistical Methods:

No statistics were performed.

Results**Recruitment/ Number analysed:**

Thirty-four children underwent colonoscopy and were included. Four patients were excluded because they did not receive the two day regimen of bisacodyl. The children were aged 18 months to 15 years, mean age 8.9 years (SD: 4.2years).

Baseline data:

Not presented.

Pharmacokinetic results:

None presented.

Efficacy results:

At colonoscopy the colon was entirely clear in 26 children (86.6%; grade I). Some stool was present in four children (13.3%; grade II) but this could be removed via the colonoscope and adequate visualisation of bowel mucosa was achieved. The frequency of bowel motions doubled while taking bisacodyl with a mean of 4-9 (range 3-13) bowel motions per day compared with a mean 2-6 (range 1-8) bowel motions per day before treatment.

Safety results:

Eight children complained of abdominal pain or cramps after bisacodyl, however abdominal pain was present before preparation. There was no exacerbation of pain even in those children with inflammatory bowel disease. One child had a single episode of faecal soiling on the second day of treatment with bisacodyl.

Discussion

Data from this open study suggest that bisacodyl 5-10 mg for 2 days prior to colonoscopy in combination with a phosphate enema on the day of examination is effective for visualising the bowel mucosa in children.

10. Forsythe WI, Kinley JG. Bowel control of children with spina bifida. *Develop Med Child Neurol* 1979;12:27.

A retrospective study describing the authors' experience with different treatments of bowel dysfunction in 47 children with meningomyelocele. Twenty-five children were treated with bisacodyl suppositories, and only 3 obtained normal bowel control and were able to stop treatment after 6 months. Sixteen children were treated with oral bisacodyl, and 8 of these obtained normal bowel control for more than 2 years.

Discussion

An old methodologically insufficient retrospective study suggesting that especially oral bisacodyl in older children with meningomyelocele may be effective in regulating bowel habits.

11. Coelho WD et al. Preparo reto-colico pelo diacetoxi-difenil-piridil-pentano para exams proctologicos em criancas. *Folha Med* 1967;55:399.

The article is in Portuguese, and not translated.

12. Aue H. Klinische Erfahrungen mit einem Kontaktlaxativum bei Kindern und Jugendlichen. *Die Medizinische* 1955;3:118.

The article is in German, and not translated.

13. Portorreal A and Kawakami E. Intestinal preparation for colonoscopy with oral bisacodyl and phosphate enema in children and adolescents. *GED* 2001;20:11.

Article in Spanish, abstract in English. The study included 17 children aged 10 months to 15 years and 10 months. Children 5 years and older were given bisacodyl orally, 5 and 10 mg, in the morning for two days before colonoscopy, and a phosphate enema was given at the morning before endoscopy. Bowel preparation was considered excellent in 53 %, good in 29 % and poor in 18 %. The authors conclude that bowel preparation was adequate in 8 out of 10 children.

Discussion

Data are too insufficiently presented to judge the validity of the results.

- 14. El-Baba MF et al. A prospective study comparing oral sodium phosphate solution to a bowel cleansing preparation with nutrition food package in children. J Pediatr Gastroenterol Nutr 2006;42:174.**

Description

Randomised single blind study of the effect of 2 bowel cleansing programs of which one as part of its program includes bisacodyl.

Methods

Objective(s):

The aim of the study was to evaluate the adequacy and acceptance of a pre-packaged food kit and a magnesium citrate/bisacodyl laxative for colonoscopy in children compared to standard preparation with oral sodium phosphate.

Study design:

Randomized and single-blind.

Study population /Sample size:

Patients between 4-18 years of age undergoing elective colonoscopy. No power calculations are made.

Treatments:

One group of the children (Group 1) received a pre-packaged low residue solid and liquid food kit (containing vanilla shake, lemon drink, energy bar, apple sauce, potato poppers and noodle soup) and a magnesium citrate and bisacodyl laxative kit. Children were instructed to eat the foods in the kit up to 5 pm the day before colonoscopy. The magnesium, bisacodyl laxative consisted of magnesium citrate powder, oral bisacodyl tablets and bisacodyl suppository. Magnesium citrate was mixed with water and ingested at 6 pm the day before the procedure. Oral bisacodyl was taken at 8 pm the evening prior to procedure. Dosages were: ≥ 12 years 20 mg; ≥ 8 -<12 years 15 mg; 4-<8 years 10 mg. A bisacodyl suppository was administered on the day of the procedure, dose ≥ 12 years 10 mg; <12 years 5 mg. The other group (Group 2) received clear liquids on the day prior to colonoscopy, and 45 ml of sodium phosphate solution mixed with an equal amount of water was administered at 3 pm and 6 pm followed by clear liquids until bedtime.

Outcomes/endpoints:

Adequacy of preparation graded on a five point scale during colonoscopy. A rating of the acceptance of the preparations was performed. Adverse effects were assessed.

Statistical Methods:

Fisher's exact test to test proportional differences and Wilcoxon to compare study regimens across all ratings.

Results

Recruitment/ Number analysed:

Sixty-two children participated (Group 1: n = 36, average age: 12 years. Group 2: n = 26, average age 13 years).

Baseline data:

The 2 groups were comparable with respect to demographics: age, sex, and ethnicity.

Pharmacokinetic results:

None presented.

Efficacy results:

At colonoscopy the endoscopist's rating of the bowel preparations was in favour of Group 1. The rating was excellent in 50 % in Group 1 compared to 19 % in Group 2 (P = 0.013). A significantly greater proportion of patients in Group 2 had moderate to large amounts of retained faeces compared to Group 1 (P = 0.013). Comparison of regimens across all observed ratings revealed that the adequacy of preparations was significantly different in each group.

Safety results:

The frequency of reported side effects in Group 1 was lower than in Group 2. Specific side effects are not reported.

Discussion

The results from this relatively large single-blind study suggest that bisacodyl can be included in an effective bowel cleansing program, however does not test the effect of bisacodyl in itself. Note the unexplained large difference (36 vs. 26) in the number of included children.

15. Roth van W. Pharmakokinetik und laxierende Wirkung von Bisacodyl nach Gabe verschiedener Zubereitungsform. *Arzneim.-Forsch./Drug Res* 1988;38:570.

Article in German, abstract in English. The study did not include children.

Rapporteur's comments

The studies suggest that the bisacodyl increases and improves HAPC in children with spontaneous HAPC, but not always in children without spontaneous HAPC. Spontaneous HAPCs are probably related to stool propulsion. Bisacodyl challenge may be helpful as a diagnostic tool. The studies demonstrate that bisacodyl can be included in a bowel cleansing regimen. It should be mentioned that there are no randomized studies presented to examine the longer-term effect on bowel habits of bisacodyl in children with constipation.

Guerbet

No sponsored studies have been submitted

The MAH has enclosed copies of the following publications after a search of the literature:

11. Abubakar K et al. Preparing the bowel for colonoscopy. *Arch Dis Child* 1995;73:459.

Presented above.

12. **Bassotti G et al. Endoluminal instillation of bisacodyl in patients with severe (slow transit type) constipation is useful to test residual colonic propulsive activity. Digestion 1999;60:69.**

The study includes adult patients only.

13. **El-Baba MF et al. A prospective study comparing oral sodium phosphate solution to a bowel cleansing preparation with nutrition food package in children. J Pediatr Gastroenterol Nutr 2006;42:174.**

Presented above.

14. **Godbole PP et al. Idiopathic megarectum in children. Eur J Pediatr Surg 2001;11:48.**

Presented above.

15. **Hamid SA et al. Bisacodyl and high-amplitude-propagating colonic contractions in children. J Pediatr Gastroenterol Nutr 1998;27:398.**

Presented above.

16. **Kiely EM et al. Antegrade continence enemas in the management of intractable faecal incontinence. J R Soc Med 1995;88:103P.**

Twenty-seven children (mean age 8.6 years) with intractable faecal incontinence, underwent surgery to fashion a conduit for antegrade continence enema administration (ACE). Follow up ranged from 5 to 39 months. Once technical problems had been overcome and individual ACE regimes established, the majority of the patients (89%) had a satisfactory to excellent result to ACE administration.

Discussion

The authors describe their experience with the surgery for ACE conduits only. There are no data on bisacodyl.

17. **Pinfield A, Stringer MD. Randomised trial of two pharmacological methods of bowel preparation for day case colonoscopy. Arch Dis Child 1999;80:181.**

Presented above.

18. **Portorreal A, Kawakami E. Intestinal preparation for colonoscopy with oral bisacodyl and phosphate enema in children and adolescents. GED 2001;20:11.**

Presented above.

19. **Shaoul R, Haloon L. An assessment of bisacodyl-based bowel preparation for colonoscopy in children. J Gastroenterol 2007;42:26.**

Presented above.

20. **van den Berg MM et al. Colonic manometry as predictor of cecostomy success in children with defecation disorders. J Pediatr Dis 2006;41:730.**

Presented above.

Rapporteur's comments

Since the studies are the same as those submitted by Boehringer Ingelheim, see above

ICN Polfa Rzeszow

The MAH has submitted 2 in-house reports:

1. Clinical assessment of Bisacodyl of Polfa for oral administration.

55 children (aged 3 months to 14 years) received bisacodyl in 3 forms: tablets (in infants and children >3 years of age, dragees soluble in the small intestine, and dragees soluble in the large intestine. Indications were constipation from: neurogenic bowel dysfunction; Hirschsprung's disease; habitual constipation; rickets; hypothyroidism; and Down's syndrome. The usefulness of the drug in the preparation of the gastrointestinal tract for radiographic diagnostic was also evaluated. Tests of urine, blood count, and liver blood tests were performed, however results from these tests are not revealed.

Efficacy of the tablets was described as very good. In 85% of the children < 3 years of age evacuations occurred soon, in 2-3 hours after administration of the drug. In 7% of cases the effect of drug administration occurred later, within 4-5 hours. The remaining 8% of cases were the children with Hirschsprung's disease where bisacodyl was found to be ineffective. In the older children, who took the whole dragees, the effects after administration of dragees soluble in the small intestine and soluble in the large intestine were compared. Efficacy of both forms of dragees was almost identical. The effects of the administration of dragees soluble in the large intestine were: in about 78% good, and in 22% poor or no effects. The effects of the administration of dragees soluble in the small intestine were as follows: about 70% positive effects and about 30% poor or no effects. Good efficacy of the drug was found, if evacuation occurred in 7-10 hours after administration of the drug. Stools were loose, non-diarrheal. The poor effect group comprised cases, in which evacuation occurred significantly later, stools were dense and irregular, in spite of prolonged administration of Bisacodyl. The poor effects and no effects of the application of Bisacodyl dragees occurred mostly in the children who had constipation related to the neurogenic bowel dysfunction.

Oral bisacodyl was advantageous in the preparation of the patient for urography. When administered 10-12 hours before examination, it helped to completely evacuate the gastrointestinal tract and remove intestinal gases, especially in infants.

No vomiting was observed, while in the older children administration of the tablets was very often (90% of cases) accompanied with the occurrence of unpleasant symptoms: nausea, pressure on the stomach area, belching.

Rapporteur's comments

It is not possible to judge the results of the study, due to the insufficiently described methodology. The study can hardly be used to argue for clinical efficacy and safety of bisacodyl in the paediatric patient.

2. Usefulness of Bisacodyl dragees for preparation of patients for radiographic procedures

The study tested the usefulness of bisacodyl dragees soluble in the small intestine and dragees soluble in the large intestine, in the preparation for radiographic examination. The observations involved 152 patients (including 58 inpatients and 94 outpatients), who underwent in total 352 radiographic examinations. Their age ranged from 9 to 80 years. The largest group (105 patients) comprised of patients aged from 30 to 60 years.

Rapporteur's comment

The study did include some paediatric patients; however results from paediatric patients are not presented.

No additional studies were submitted

Post-marketing safety surveillance.

One MAH has supplied a summary of adverse reactions which takes account of adverse reactions with bisacodyl tablets and suppositories covering the period 28.04.2005-27.04.2008 covering 1,694,053,819 DDDs for tablets, 98,896,999 DDDs for suppositories 10 mg and 3,549,986 DDDs for suppositories 5 mg.

Adverse drug reactions (ADRs) from medication errors have been reported in 5 children. The MAH concludes that only listed non-serious ADRs were reported. There was 1 case (16 year old girl with eating disorder) of drug abuse reported. No adverse events were reported for this case. Otherwise no summary specifics for infants and children are presented.

The MAH concludes that the safety data presented did not identify new safety issues associated with the use of bisacodyl, and that the benefit risk profile remains unchanged and favourable.

One MAH has submitted PSUR for the period 14.11.2001-30.11.2006 covering 304,626,750 DDDs. There were no spontaneous adverse drug reactions reported and no reports from regulatory authorities were received.

One MAH has not submitted PSUR-data.

Rapporteur's comment

2 MAHs have provided post-marketing safety surveillance data; however not specifically concerned with children. The data suggest that bisacodyl has the same safety profile in the paediatric population compared to the adult population.

RAPPORTEUR'S PPdAR OVERALL CONCLUSION AND RECOMMENDATION**➤ Overall conclusion**

Based on the review of the presented paediatric data on safety and efficacy, the rapporteur considers that the benefit risk ratio is in favour to maintain an indication for oral and rectal bisacodyl in the paediatric age group.

➤ **Recommendation**

For consistency between bisacodyl containing products across the EU, it is recommended that the SmPC contains the following:

For orally and rectally administered bisacodyl

4.2 Posology and administration

Children aged 10 years or younger with chronic constipation should only be treated under the guidance of a physician. Bisacodyl should not be used in children aged 2 years or younger.

Short-term treatment for constipation:

Adults and children over 10 years:

1 - 2 coated tablets (5 - 10 mg) daily before bedtime, or

1 suppository (10 mg) for immediate effect.

Children 2 - 10 years: *1 coated tablet (5 mg) daily before bedtime, or*

1 suppository (5 mg) for immediate effect.

For preparation of diagnostic procedures and preoperatively

Should only be used under medical supervision.

Adults and children over 10 years

2 coated tablets (10 mg) in the morning and 2 coated tablets (10 mg) in the evening and 1 suppository on the following morning is recommended.

Children 4-10 years of age: *1 coated tablet (5 mg) in the evening and one suppository (5 mg) on the following morning is recommended.*

Due to the specific pharmaceutical form of the product from Guerbet (bottle containing a phosphate laxative and 4 (5 mg each) film-coated bisacodyl tablets for use as bowel preparation specifically for adults, the present posology should be maintained (*For adults only. Do not administer to children below the age of 15 years*).

COMMENTS FROM MEMBER STATES AND MAH RESPONSES

The following responses to the preliminary assessment report for paediatric studies submitted in accordance with article 45 of regulation (EC) 1901/2006 for Bisacodyl have been received:

MS comment:

The overall conclusions of the RMS are endorsed. Clarification should, however, be sought on the following matter:

One of the MAHs, Boeinger Ingelheim, has recently reported to the MS (letter as of 20th January, 2009) that one of its bisacodyl containing products, being newly approved in Australia, has been restricted by the TGA to the age group “older than 6 years of age”, which is in contrast to the previously known facts/practices and to the conclusion of the RMS in this procedure. The MAH should therefore be asked to make fully available the reasons for the decision of the Australian agency and especially display whether the Australian authorities have based their decision of restriction of age groups on specific data, e.g. regarding increased rates of undesirable effects in young children.

Boehringer Ingelheim response:

The above mentioned restriction by the Australian Agency to adults and children older than 6 years of age concerns the bisacodyl 5 mg tablets. It is related to the dosage form „tablets“ not to the active ingredient as such, because the Medicines Evaluation Committee (MEC) advises that few 3 or 4 year old children can swallow solid dosage forms, and therefore fear that there is a risk for young children to inhale the product.

With the 5 mg suppositories another dosage form for this age group is available (for children 4 to 10 years of age, and under 4 years of age on medical advice).

For BI’s opinion, please refer to the response to the comments below.

Rapporteur’s comment

The MAH has already reported on this matter. It seems that the reason for the age limit of 6 years is that the MEC advises that few 3 or 4 year old children may risk inhalation/aspiration of solid dosage forms. No evidence in the scientific literature has been submitted to support this concern, and there are no reported events of inhalation/aspiration of bisacodyl tablets in children despite its use for some 50 years.

MS comment:

For rectally administered bisacodyl:

Given that no paediatric indication is currently granted in the MS for the suppositories of bisacodyl, the poor level of clinical demonstration currently provided is far from being adequate for considering any paediatric statement in the SPC of suppositories, whatever the indication is considered (short-term symptomatic treatment of constipation or bowel cleansing). If some degree of extrapolation between both conditions in adults and paediatric patients could be acknowledged, at least a valid demonstration to support the dose regimen for the suppositories should have been required in both indications which is not the case currently. Such a demonstration should be requested in the scope of a further article 46.

For orally administered bisacodyl:

Due to the risk of inadvertent aspiration, oral solid formulations should normally be contra-indicated in children under 6 years of age, which is the case for the oral tablets of bisacodyl in France. A more appropriate and suitable oral formulation for this paediatric population may be further taken under consideration in the scope of a further article 46.

We understand that the MS position might differ to those member states having already granted paediatric indications and doses regimens and for whom the data submitted as part of the article 45 are not even compulsory. However, such a position cannot be reversed given the above consideration.”

Boehringer Ingelheim response:

For rectally administered bisacodyl:

In the MS, only suppositories containing 10 mg of bisacodyl are currently registered. According to the CCDS of the MAH this strength is only recommended for adults and children over 10 years of age. No age lowering is requested by the MAH for this formulation (suppositories 10mg). Instead, for children suppositories containing 5 mg bisacodyl are recommended in those countries where available.

For orally administered bisacodyl:

BI disagrees with this restriction for the tablets for the following reasons:

- Tablet size and presentation:
When compared with solid dosage forms currently available on the market for use in children, the tablet size of Dulcolax tablets is very small (average diameter: 6 mm, average thickness: 3.5 mm). In addition, Dulcolax tablets are sugar-coated. Both characteristics facilitate the swallowing of Dulcolax tablets.
- Clinical evidence of the use of bisacodyl tablets in children under 6 years of age: The paediatric use of bisacodyl tablets has been evaluated in several clinical trials, including children under 6 years of age. Difficulty swallowing the Dulcolax tablets was not documented when administered to children under 6 years of age.
- Post-marketing experience (more than 50 years):
Boehringer Ingelheim is not aware of any established reports/complaints in relation to difficulty swallowing the Dulcolax tablets in children.

Rapporteur's comment

The rapporteur does not agree with the MS position that insufficient data are available for rectal bisacodyl in the paediatric age group. The studies, of which many have used rectal administration of bisacodyl, have been reviewed and discussed in the preliminary assessment report. These studies concurrently demonstrate a beneficial effect of bisacodyl suppositories on paediatric constipation. With respect to the age limits for oral bisacodyl, see the argumentation above.

MS comment:

The MS overall agrees with the rapporteur's conclusion and recommendation, in the PAR, with the exception of the lower age limit for treatment of short term constipation and treatment of chronic constipation, which should be increased from 2 years to 4 years, as is currently authorised. There is insufficient data to support the lowering of the age limit.

Boehringer Ingelheim response:

There were at least 132 children under the age of 4 years studied in the several reports and publications. They are mentioned in the Clinical Overview. No further clinical data are available to support the lowering of the age limit.

Rapporteur's comment

Many studies have included children less than 4 years of age, and all have shown a beneficial effect of bisacodyl in this age group (see preliminary assessment report). Also, there is no physiological basis to suggest that the 2-4 years old should differ from the children older than 4 years of age with respect to the effect of bisacodyl on constipation.

ICN Polfa Rzeszow comment:

In our opinion, due to the risk of inadvertent aspiration, oral solid formulations should not be administered to children under 4 years of age and therefore the lower age limit for oral preparations of bisacodyl should be 4 years.

Rapporteur's comment

See argumentation above.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION**➤ Overall conclusion**

It is the rapporteur's conclusion that, based on the available scientific literature, the indications for bisacodyl in the paediatric age group should be maintained as put forward in the preliminary assessment report.

➤ Recommendation

For consistency between bisacodyl containing products across the EU, it is recommended that the SmPC contains the following:

For orally and rectally administered bisacodyl

4.2 Posology and administration

Children aged 10 years or younger with chronic constipation should only be treated under the guidance of a physician. Bisacodyl should not be used in children aged 2 years or younger.

Short-term treatment for constipation:

Adults and children over 10 years:

1 - 2 coated tablets (5 - 10 mg) daily before bedtime, or

1 suppository (10 mg) for immediate effect.

Children 2 - 10 years: *1 coated tablet (5 mg) daily before bedtime, or*

1 suppository (5 mg) for immediate effect.

For preparation of diagnostic procedures and preoperatively

Should only be used under medical supervision.

Adults and children over 10 years

2 coated tablets (10 mg) in the morning and 2 coated tablets (10 mg) in the evening and 1 suppository on the following morning is recommended.

Children 4-10 years of age: *1 coated tablet (5 mg) in the evening and one suppository (5 mg) on the following morning is recommended.*

Due to the specific pharmaceutical form of the product from Guerbet (bottle containing a phosphate laxative and 4 (5 mg each) film-coated bisacodyl tablets for use as bowel preparation specifically for

adults, the present posology should be maintained (*For adults only. Do not administer to children below the age of 15 years*).

DISCUSSIONS ON SmPC FOLLOWING CIRCULATION OF FINAL AR

Following circulation of the final assessment report, comments were received from two MS that the harmonised paediatric posology as proposed by the Rapporteur could not be accepted. It is the Rapporteurs opinion that agreement on a fully EU harmonised paediatric posology can not be achieved in this particular case, because of differences that is exist in the already approved paediatric posology/differences in approved strengths of bisacodyl among MS.

The procedure is concluded in accordance with the Rapporteur's final recommendation for paediatric posology (see above) and implementation of the harmonised posology in MS via type II variation is recommended. However, we acknowledge that a few MS is not in agreement with the proposed changes. In these MS it may be relevant to implement only relevant parts of the proposed harmonised paediatric posology, to maintain the nationally approved age limit for paediatric use or to retain the Product Information which is currently authorised in that particular MS.

The Rapporteur recommends that the MAH achieve full harmonisation regarding paediatric use through use of appropriate regulatory procedures.