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

Simeticone

Disflatyl

UK/W/0084/pdWS/001

Rapporteur:	United Kingdom (UK)
Finalisation procedure (day 120):	21.02.2017

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Disflatyl
INN (or common name) of the active substance(s):	Simeticone
MAH (s):	See section IX.
Pharmaco-therapeutic group (ATC Code):	A02DA01
Pharmaceutical form(s) and strength(s):	Oral drops, 40mg/ml

I. EXECUTIVE SUMMARY

On 18th March 2016 the MAH submitted fifty completed studies for simeticone, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for simeticone and that there is no consequential regulatory action. A line listing has also been included as per the procedural guidance.

Simeticone products are available across the EU and are indicated for use in children for the symptomatic relief of dyspepsia, heartburn, flatulence, gripping pain and infantile colic. The majority of simeticone products available in the UK are indicated for use in children aged older than 12 years, with only one product as an oral suspension (40mg/ml) being indicated for use in infants (no age specified). The posology for infants is 20mg to 40mg (0.5 – 1.0 ml) administered before each feed. One tablet and two capsule formulations of simeticone are available in the UK, with posology varying from 100 – 125mg taken three to four times a day by children aged over 12 years.

II. RECOMMENDATION

The efficacy data presented have significant limitations so it is not possible to draw any conclusions on the efficacy, or otherwise, of simeticone for use in any paediatric indication. The rapporteur therefore concludes that based on the data submitted for assessment under this Article 45 procedure, no changes are deemed necessary in the approved paediatric indications.

It is not possible to reach any conclusion on the safety of simeticone from the data presented in the submitted papers as these studies do not provide sufficient information regarding any new potential adverse events specific to the paediatric population. The MAH provided additional data on adverse events in children associated with the use of simeticone based on their pharmacovigilance database; following this submission, no new safety concerns were identified.

The rapporteur concludes that, following this work sharing procedure, simeticone's benefit:risk ratio in the paediatric population remains unchanged.

Summary of outcome

- ☒ No change
- ☐ Change
- ☐ New study data: <section(s) xxxx, xxxx>
- ☐ New safety information: <section(s) xxxx, xxxx>
- ☐ Paediatric information clarified: <section(s) xxxx, xxxx>
- ☐ New indication: <section(s) xxxx, xxxx

III. INTRODUCTION

On 18th March 2016 the MAH submitted fifty completed studies for simeticone, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for simeticone and that there is no consequential regulatory action.

A line listing has also been included as per the procedural guidance.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical studies

Simeticone, also known as simethicone, is a mixture containing hydrated silica gel and a polymer of 200-350 units of dimethylsiloxane (dimethicone). Either simeticone or dimethicone were used in the studies discussed in this report, however the posology used varied between studies.

Assessor's comment:

A number of simeticone products are available across the EU and are indicated for use in children for the symptomatic relief of dyspepsia, heartburn, flatulence, gripping pain and infantile colic. The majority of simeticone products available in the UK are indicated for use in children aged older than 12 years.

There are four products in the UK that are indicated for use under the age of 12 years. Two products are indicated for use in infants; one product as oral drops, emulsion (100mg/ml) and one as oral suspension (40mg/ml). However no specific age range is mentioned in the SmPC of these products. The other products are indicated for children 1-18 years of age.

One capsule and three tablet formulations of simeticone are available in the UK, with posology varying from 100 – 125mg taken three to four times a day by children aged over 12 years. There is one additional capsule product containing 100mg of simeticone per capsule that is indicated for use in children with no specific age range mentioned in the SmPC.

IV.2 Clinical aspects

1. Introduction

The MAH submitted reports of and a synopsis for the following published articles:

1. Lesperance MM. A pediatric otolaryngologist learns to diagnose acute otitis media. Arch Otolaryngol Head Neck Surg. August 1, 2007, 745-6
2. Barkun A. Commonly used preparations for colonoscopy: Efficacy, tolerability and safety - A Canadian association of gastroenterology position paper. Can J Gastroenterol, November 1, 2006, 699-710
3. Coco TJ, King WD, Slattery AP. Descriptive epidemiology of infant ingestion calls to a regional poison control center. South Med J. August 1, 2005, 779-83)
4. Chitkara DK et al. Aerophagia in children: Characterization of a functional gastrointestinal disorder. Neurogastroenterol Motil. August 1, 2005, 518-22
5. Connor F. Gastrointestinal complications of fundoplication. Curr Gastroenterol Rep. June 1, 2005, 219-26
6. Orenstein SR et al. Nizatidine for the treatment of pediatric gastroesophageal reflux symptoms: An open-label, multiple-dose, randomized, multicenter clinical trial in 210 children. Clin Ther. April 1, 2005, 472-83
7. Ota FS, Abramo TJ, Maxson RT. Ominous findings in toddlers with increasing abdominal girth: Two unusual cases and a review of the clinical evaluation. Ann Emerg Med. May 1, 2005, 517-23
8. Garg P. Infantile colic – Unfolded. Indian J Pediatr. October 1, 2004, 903-6
9. Perez A, Scribano PV, Perry H. An intentional opiate intoxication of an infant: When medical toxicology and child maltreatment services merge. Pediatr Emerg Care. November 1, 2004, 769-72
10. Besedovsky A, Li BUK. Across the developmental continuum of irritable bowel syndrome: Clinical and pathophysiologic considerations. Curr Gastroenterol Rep. June 1, 2004, 247-53
11. Spiro DM et al. Association between antibiotic use and primary idiopathic intussusception. Arch Pediatr Adolesc Med. January 1, 2003, 54-9
12. Ball R et al. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: Reports to the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J. March 6, 2001, 219-23
13. Garrison MM et al. Early childhood: Colic, child development, and poisoning prevention. A systematic review of treatments for infant colic. Pediatrics. July 1, 2000, 184-90
14. Voepel-Lewis TD et al. Evaluation of simethicone for the treatment of postoperative abdominal discomfort in infants. J Clin Anesth. March 1, 1998, 91-4
15. Sferra TJ, Heitlinger LA. Gastrointestinal gas formation and infantile colic. Pediatr Clin North Am. May 7, 1996, 489-510
16. Treem WR. Infant colic: A pediatric gastroenterologist's perspective. Pediatr Clin North Am. November 11, 1994, 1121-38
17. Bartel DR et al. Sclerodermalike esophageal disease in children of mothers with silicone breast implants. J Am Med Assoc. September 20, 1994, 767-70
18. Danielsson B, Hwang CP. Treatment of infantile colic with surface active substance (Simethicone). Acta Paediatr Scan. October 2, 1985, 446-50
19. Savino F et al. Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. Pediatrics. 2007 Jan;119(1):e124-30
20. Ge ZZ et al. The role of simeticone in small-bowel preparation for capsule endoscopy. Endoscopy. 2006 Aug;38(8):836-40
21. Tsou VM et al. Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with gastroesophageal reflux disease (GERD). Clin Pediatr (Phila). 2006 Oct;45(8):741-9
22. Savino F et al. Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula. Eur J Clin Nutr. 2006 Nov;60(11):1304-10

23. Albert J et al. Simethicone for small bowel preparation for capsule endoscopy: a systematic, single-blinded, controlled study. Gastrointest Endosc. 2004 Apr;59(4):487-91
24. de la Portilla F et al. Improved quality of anorectal endoluminal ultrasonography using emulsion of dimethicone. Dis Colon Rectum. 2003 Oct;46(10):1436-7
25. Wiberg JM, Nordsteen J, Nilsson N. The short-term effect of spinal manipulation in the treatment of infantile colic: a randomized controlled clinical trial with a blinded observer. J Manipulative Physiol Ther. 1999 Oct;22(8):517-22
26. Lucassen PL et al. Effectiveness of treatments for infantile colic: systematic review. BMJ. 1998 May 23;316(7144):1563-9
27. Corazziari E et al. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. Dig Dis Sci. 1996 Aug;41(8):1636-42
28. Metcalf TJ et al. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. Pediatrics. 1994 Jul;94(1):29-34
29. Sethi KS, Sethi JK. Simethicone in the management of infant colic. Practitioner. 1988 May 9;232(1448):508
30. Lifschitz CH, Irving CS, Smith EO. Effect of a simethicone-containing tablet on colonic gas elimination in breath. Dig Dis Sci. 1985 May;30(5):426-30
31. Bowring AR, Mackay D, Taylor FR. The treatment of napkin dermatitis: a double-blind comparison of two steroid-antibiotic combinations. Pharmatherapeutica. 1984;3(9):613-7
32. Hodgkinson R et al. Comparison of cimetidine (Tagamet) with antacid for safety and effectiveness in reducing gastric acidity before elective cesarean section. Anesthesiology. 1983 Aug;59(2):86-90
33. Korman MG et al. Influence of smoking on healing rate of duodenal ulcer in response to cimetidine or high-dose antacid. Gastroenterology. 1981 Jun;80(6):1451-3
34. Brouwers JR et al. A controlled trial of senna preparations and other laxatives used for bowel cleansing prior to radiological examination. Pharmacology. 1980;20 Suppl 1:58-64
35. Suoranta H, Standertskjöld-Nordenstam CG, Lähde S. The value of simethicone in abdominal preparation. Radiology. 1979 Nov;133(2):307-8
36. Almeyda JJ et al. "Timodine" cream in the treatment of flexural dermatoses and napkin rash. Practitioner

The line listing for this procedure also included the following references which were not provided by the MAH, but have been obtained independently by the Rapporteur:

1. Bruhn C. Diseases of the gastrointestinal tract and the skin in children - Part 7. Dtsch Apoth Ztg. September 13, 2007, 66-76
2. McCollough M, Sharieff GQ. Abdominal pain in children. Pediatr Clin North Am. February 1, 2006, 107-37
3. Leung AKC, Lemay JF. Infantile colic: A review. J R Soc Promot Health. July 1, 2004, 162-6
4. Gervais AA. Pediatric health: Colic. Can Pharm J. September 1, 1996, 27-8
5. Sofo L et al. SELG-simeticone vs standard preparation in patients undergoing an endoscopic examination of large bowel. G Ital Endosc Dig. May 29, 1995, 37-42
6. Nykamp D. Nonprescription medications in the pediatric population. Am Pharm. May 3, 1995, 10-27
7. Armstrong KL, Fraser DKB, Faoagali JL. Gastrointestinal bleeding with influenza virus. Med J Aust. March 11, 1991, 180-2)
8. Gaburro D, Burlina A. Management of acute infectious diarrhea in childhood. Riv Ital Pediatr. December 1, 1985, 122-7
9. Hanauer SB et al. Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone versus loperamide alone and simethicone alone in the

treatment of acute diarrhea with gas-related abdominal discomfort. Curr Med Res Opin. 2007 May;23(5):1033-43
10. Yang JC et al. The role of gastric acid and Helicobacter pylori in the natural course of duodenal ulcer. J Microbiol Immunol Infect. 1999 Sep;32(3):155-62
11. Kark W, Krebs-Richter H, Hotz J. Improving the effect of orthograde colonic lavage with golytely solution by adding dimethicone. Z Gastroenterol. 1995 Jan;33(1):20-3
12. Friis H. Dimethicone in lactulose-induced dyspepsia. Effect on H2 production and Symptoms. Ugeskr Laeger. 1993 Oct 18;155(42):3378-80
13. Simón A et al. The use of gastric ultrasonography in the evaluation of a new antiflatulent preparation in human volunteers. Methods Find Exp Clin Pharmacol. 1985 Jul;7(7):393-8
14. Sherbaniuk RW et al. Comparative study of cimetidine and Mylanta II in the 6-week treatment of gastric ulcer. J Clin Gastroenterol. 1985 Jun;7(3):211-5

2. Clinical studies

The studies included in the line listing have been grouped for assessment by the following headings;

1. Papers relating to use as bowel preparation,
2. Papers relating to use in infantile colic,
3. Papers relating to other uses,
4. Papers relating to safety,
5. Papers not in English, and
6. Papers that do not focus on the use of simeticone.

Papers relating to use in infantile colic

a) McCollough M, Sharieff GQ. Abdominal pain in children. Pediatr Clin North Am. February 1, 2006, 107-37
b) Garg P. Infantile colic – Unfolded. Indian J Pediatr. October 1, 2004, 903-6
c) Besedovsky A, Li BUK. Across the developmental continuum of irritable bowel syndrome: Clinical and pathophysiologic considerations. Curr Gastroenterol Rep. June 1, 2004, 247-53
d) Leung AKC, Lemay JF. Infantile colic: A review. J R Soc Promot Health. July 1, 2004, 162-6
e) Garrison MM et al. Early childhood: Colic, child development, and poisoning prevention. A systematic review of treatments for infant colic. Pediatrics. July 1, 2000, 184-90
f) Gervais AA. Pediatric health: Colic. Can Pharm J. September 1, 1996, 27-8
g) Sferra TJ, Heitlinger LA. Gastrointestinal gas formation and infantile colic. Pediatr Clin North Am. May 7, 1996, 489-510
h) Treem WR. Infant colic: A pediatric gastroenterologist's perspective. Pediatr Clin North Am. November 11, 1994, 1121-38
i) Danielsson B, Hwang CP. Treatment of infantile colic with surface active substance (Simethicone). Acta Paediatr Scan. October 2, 1985, 446-50
j) Savino F et al. Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. Pediatrics. 2007 Jan;119(1):e124-30
k) Savino F et al. Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula. Eur J Clin Nutr. 2006 Nov;60(11):1304-10

l) Wiberg JM, Nordsteen J, Nilsson N. The short-term effect of spinal manipulation in the treatment of infantile colic: a randomized controlled clinical trial with a blinded observer. J Manipulative Physiol Ther. 1999 Oct;22(8):517-22
m) Lucassen PL et al. Effectiveness of treatments for infantile colic: systematic review. BMJ. 1998 May 23;316(7144):1563-9
n) Metcalf TJ et al. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. Pediatrics. 1994 Jul;94(1):29-34
o) Sethi KS, Sethi JK. Simethicone in the management of infant colic. Practitioner. 1988 May 9;232(1448):508

Assessor's comment:

Paper (i) is a double-blind cross-over study of simeticone in the treatment of infantile colic in 27 patients. Seven days of simeticone or placebo were followed by a 4 day washout period and then 7 days in the crossover arm of the trial. The study used interviews, 24 hours records and behavioural observations to demonstrate efficacy endpoints. No benefit over placebo was demonstrated, and a high rate of placebo-responsiveness was observed. Adverse events or safety concerns during the trial were not reported in this paper.

Paper (m) is a randomised double-blind placebo-controlled crossover trial of simeticone in the treatment of infantile colic with 83 infant subjects. Between 3 and 10 days of simeticone or placebo were followed by immediate crossover into the opposite arm of the trial for a further 3 to 10 days in the crossover arm of the trial. Daily diaries of events were recorded as well as a daily score by the caregiver of their child's symptoms on a 5 point scale and an overall score by the caregiver at the end of each treatment arm. No statistically significant difference was observed between the two treatments for the treatment of infantile colic generally or the treatment of gas-related symptoms only. Adverse events or safety concerns during the trial were not reported in this paper.

Paper (o) is a double-blind, placebo-controlled crossover trial of simeticone. Seven days of simeticone or placebo were followed by immediate crossover into the opposite arm of the trial for a further 7 days in the crossover arm of the trial. Twenty-six infants were recruited. A daily diary was used to record frequency of crying attacks and to grade the severity of crying attacks on a 4-point scale. Parents were also asked to record the number, nature and consistency of the infant's stools and any perceived adverse effects. At the end of the study, parents were asked to indicate, if possible, in which trial period the most effective control of symptoms was observed. Significant differences between frequency and severity of attacks were observed between active and placebo arms after four days on treatment. Twenty out of 26 patients' parents considered active treatment more effective than placebo. No adverse events were noted in the trial.

Paper (e) is a systematic review of treatments for infantile colic. It reviews 3 randomised controlled trials of simeticone in this condition, those by Sethi, Danielsson and Metcalf (Papers (o), (i) and (n) respectively). Only the study by Sethi demonstrated a benefit to treatment with simeticone. The authors conclude that this existing data does not demonstrate conclusive benefit of simeticone as a treatment for infantile colic. Paper (g) is a review article on gastrointestinal gas formation and infantile colic. It cites the same papers as discussed in Paper (e) and concludes that simeticone does not have proven efficacy in the treatment of gas-related symptoms. Paper (m) is a systematic review of treatments for infantile colic. The review included all controlled clinical trials available from Medline, Embase and the Cochrane Controlled Trials Register at the time of writing. This report reviewed the same trials as discussed in paper (e) and reached the conclusion that simeticone was not beneficial in the treatment of this condition.

Paper (a) is a review article on abdominal pain in children which states that "*Simethicone has not been found to reduce colic.*" Paper (b) is a review article on infantile colic which also states that simeticone is not effective in this condition. No further comments regarding simeticone are made in either paper.

Paper (c) is a review article regarding Irritable Bowel Syndrome in children and adults. Simeticone is mentioned as being an active bubble-disrupting agent, which had no significant benefit when compared with placebo in infantile colic. This paper cites Lucassen PL *et al* (1998) and Metcalf TJ *et al* (1994) (Papers (m) and (n)) as sources supporting this statement.

Paper (d) is a review article regarding infantile colic which states that simeticone has been used to treat the condition with success in the study by Sethi and Sethi (1998) (i.e. Paper (o)), but that several other randomised controlled studies found simeticone no more effective for the treatment of colic than placebo. In support of the statement of no benefit over placebo, this review cites Wade S, Kilgour T, Extracts from 'clinical evidence'. Infantile colic *BMJ* 2001; 323:437-40 along with Papers (i) and (n).

Paper (f) is a review article on management of infantile colic for pharmacists. It comments that there is no convincing clinical evidence to prove its effectiveness in colic. The author also comments that as simeticone is not absorbed into the blood stream and excretion is solely through the bowels, no secondary effects or toxicity have been observed at the time of writing.

Paper (h) is a review article that cites Sethi and Sethi (1998) in support of the position that simeticone may be effective in treating infantile colic in those who swallow excessive amounts of air and pass flatus frequently. No further comment regarding simeticone is made in this paper.

Paper (j) is a trial comparing *Lactobacillus reuteri* against simeticone for the treatment of infantile colic, with simeticone acting as the control arm of the study. *Lactobacillus reuteri* was demonstrated to have significantly greater efficacy than simeticone from days 14 to 28 of treatment ($p<0.05$). No adverse effects were reported.

Paper (k) is a trial comparing a new infant formula against standard formula + simeticone for the treatment of infantile colic. The study concluded that the use of a partially hydrolysed formula supplemented with fructo- and galacto-OS induces a reduction of crying episodes in infants with colic after 7 and 14 days when compared with a standard formula and simeticone. No comment is made in the paper regarding treatment safety.

Paper (l) is a trial comparing chiropractic spinal manipulation against treatment with simeticone in the treatment of infantile colic in 50 infants. No comment is made in the paper regarding treatment safety.

The NICE Clinical Knowledge Summary on the treatment of Infantile Colic (last revised in November 2014) states that a one-week trial of simeticone drops should be considered only "if parents feel unable to cope despite advice and reassurance". The papers discussed in this report suggest that simeticone may not provide any significant benefit over placebo in the treatment of infantile colic. Nevertheless the mixed nature of study results discussed here and the low number of total study participants mean it is not possible to reach a robust conclusion on the efficacy of simeticone for this indication. The limited safety information included in these papers is not considered sufficient to reach any conclusion on the safety of simeticone.

Papers relating to use as bowel preparation

a) Barkun A. Commonly used preparations for colonoscopy: Efficacy, tolerability and safety - A Canadian association of gastroenterology position paper. Can J Gastroenterol, November 1, 2006, 699-710
b) Ge ZZ et al. The role of simeticone in small-bowel preparation for capsule endoscopy. Endoscopy. 2006 Aug;38(8):836-40
c) Suoranta H, Standertskjöld-Nordenstam CG, Lähde S. The value of simethicone in abdominal preparation. Radiology. 1979 Nov;133(2):307-8

Assessor's comment:

Paper (a) is a position paper from the Canadian Association of Gastroenterology. This paper mentions that in an effort to improve visibility of the distal small intestine in capsule endoscopy, several studies have assessed products for bowel cleansing prior to ingestion of the capsule endoscopy. The paper states that bowel preparation may change small bowel transit time and visibility, which may lead to a higher rate of complete capsule endoscopy studies and a higher diagnostic yield. This paper references a single study on simeticone for this use, the Albert *et al* (2004) paper. Albert *et al* (2004) is discussed later in the section of this report entitled "*Papers that do not focus on the use of simeticone for the approved indications in children"*.

Paper (b) is a randomised, prospective controlled study of 56 patients undergoing capsule endoscopy and the role of simeticone in small bowel preparation for this procedure. Patients were randomly allocated to groups receiving either simeticone or no simeticone, on the basis of a computer−generated random number table. Patients in the simeticone group (n = 28) received 300 mg simeticone for bowel preparation 20 min before capsule endoscopy, while patients in the non-simeticone group (n = 28) received no medication for bowel preparation. Two experienced endoscopists assessed and graded the visibility of the mucosa and intraluminal gas bubbles in a single-blinded fashion. This study recruited subjects from the ages of 5 to 77 years, with a the median age in the simeticone group being 49 years (range 16-77) and in the non-simeticone group being 42 (range 5-77). Data from the study were not stratified by age, so it is not possible to determine how many subjects recruited were children and what, if any, impact bowel preparation with simeticone had in the paediatric age range. Overall, the visibility of the mucosa in the proximal small bowel in patients who received preparation with simeticone was considered to be better, with fewer intraluminal bubbles, than in those without bowel preparation ($P < 0.025$). Inter-observer agreement was excellent ($r \geq 0.8$, $P < 0.05$). No adverse events of simeticone were observed.

Paper (c) is a double-blind study of abdominal radiographs obtained from patients aged 16 to 94 years of age to determine whether administration of dimethicone reduces the amount of gastrointestinal gas observed on imaging. 169 patients randomly received lactulose and either dimethicone or placebo the day before imaging. Patients were fasted overnight prior to imaging. The following grading system was used to grade the images obtained; 0 (no gas), 1 (a slight amount), 2 (a moderate amount), and 3 (abundant) and found that there was no statistically significant difference between the two groups. The investigators concluded that dimethicone does not reduce the amount of gas in the gastrointestinal tract and therefore has no role in preparing the patient for radiological examination of the abdomen. No comment was given in the paper regarding adverse events.

These papers suggest that simeticone may have a role in bowel preparation, however the extent to which it provides a benefit is unclear at present. Further research is required before a conclusion on the efficacy of simeticone for this indication can be reached. There is insufficient information included in these papers to reach any conclusion on the safety of simeticone.

Papers relating to other uses

a) Chitkara DK et al. Aerophagia in children: Characterization of a functional gastrointestinal disorder. Neurogastroenterol Motil. August 1, 2005, 518-22
b) Voepel-Lewis TD et al. Evaluation of simethicone for the treatment of postoperative abdominal discomfort in infants. J Clin Anesth. March 1, 1998, 91-4
c) Lifschitz CH, Irving CS, Smith EO. Effect of a simethicone-containing tablet on colonic gas elimination in breath. Dig Dis Sci. 1985 May;30(5):426-30
d) Nykamp D. Nonprescription medications in the pediatric population. Am Pharm. May 3, 1995, 10-27

Assessor's comment:

Paper (a) is a retrospective study which describes the management of 45 children aged between 1 and 17 years with a diagnosis of aerophagia at a US tertiary medical centre between 1975 and 2003. In four of these 45 patients simeticone treatment was initiated. Only 12 patients had a documented follow-up visit in their medical records, with 4 of these 12 being recorded has having an improvement in their symptoms and none reporting worsening. One of the four patients with symptomatic improvement was treated with chlordiazepoxide, aluminium hydroxide and simeticone. The other three whose symptoms improved were given education about aerophagia alone.

Paper (b) is a randomised double-blinded study of 175 children aged less than 28 months of age who underwent an inhalational anaesthetic for procedures that caused relatively little pain. The objective of the study was to determine if abdominal discomfort is a cause for distress symptoms in infants following inhalational anaesthesia and to evaluate the role of simeticone in treating this discomfort. The investigators concluded that entrapment of gas or air due to inhalational anaesthesia did cause abdominal discomfort in this patient group and that younger infants were at greatest risk for this problem. 36 infants developed abdominal discomfort post-operatively and were given either placebo (19 patients) or simeticone (17 patients). Discomfort was measured using the Faces Legs Activity Cry and Consolability (FLACC) Behavioural Pain Scale pre-drug, at 10, 20 and 30 minutes post-drug administration and at discharge. Those who received simeticone become comfortable earlier and required fewer rescue medications compared with placebo (rescue medications were administered if discomfort had not resolved within 15 minutes of administration of simeticone or placebo). Children who received placebo were significantly more likely to require rescue medications (p=0.02). There were no differences in the ability to tolerate oral fluids or length of stay post-operatively. No safety data regarding simeticone were reported in this paper. Given the small number of patients enrolled and the low power of this trial, it is not possible to conclude definitively whether the apparent benefits of simeticone treatment in this patient group are a true treatment effect.

Paper (c) is a placebo-controlled study of the effect of simeticone on colonic gas elimination in breath. The concentration of H_2 in the intestine is represented by levels of H_2 in the breath. Breath H_2 (along with H_2 in flatus) rises following ingestion of non-absorbable carbohydrate. Fifteen normal subjects aged 12 to 52 years were recruited. Subjects received lactulose, plus either two tablets of simeticone or placebo daily for two days. Breath samples were collected over a 210 minute period following ingestion of non-absorbable carbohydrate and were analysed for H_2 using gas chromatography. The time course of H_2 expiration above baseline levels were calculated and compared between the three studies. No significant differences in transit time were found. Cumulative H_2 expiration was significantly lower following treatment with simeticone compared to placebo. Simeticone reduced the amount of H_2 eliminated in breath, but this effect was partially offset by H_2 production from the fermentation of unabsorbed substances used in

the formulation of the simeticone tablets. Data from this trial was not stratified by age and, given the low number of subjects enrolled, it is not possible to determine whether a true treatment effect was observed. No comment on adverse events was made in this paper.

Paper (d) is a continuing education reference from the American Pharmaceutical Association. This reference lists simeticone under the heading “Antidiarrheals and Antiflatulents” as a frequently used non-prescription product and gives details of posology. No safety data for this product is provided.

These papers suggest that simeticone may have a role in the relief of symptoms of aerophagia and abdominal discomfort following inhalational anaesthesia, although further research is required before a conclusion on the efficacy of simeticone for these indications can be reached. There is insufficient information included in these papers to reach any conclusion on the safety of simeticone.

Papers relating to safety

a) Coco TJ, King WD, Slattery AP. Descriptive epidemiology of infant ingestion calls to a regional poison control center. South Med J. August 1, 2005, 779-83)

Assessor’s comment:

This was a retrospective study of the epidemiology of ingestion events from a US poison centre in infants aged 6 months of younger. Of 358 cases reviewed, seven cases of “therapeutic misadventure” involving simeticone were recorded. “Therapeutic misadventure” refers to unintentional overdose when administering treatment, i.e. a medication error that excludes deliberate overdose or unintentional ingestion. Simeticone was the joint the 6th most common medication involved in incidents in this age group in this study alongside amoxicillin and a zinc oxide containing diaper cream. Medications involved in a greater number of cases include ranitidine (24 cases), metoclopramide (18 cases), acetaminophen (17 cases), a combination preparation containing brompheniramine and phenylephrine as infant drops (9 cases) and hyoscyamine sulfate (8 cases).

No further details of the seven cases involving simeticone are specifically outlined in this paper. General details included in the paper were that the majority of medication misadventures recorded in the paper did not involve toxicity, with 12% of cases having ingested amounts that fell within the range of toxicity. 14% of cases were symptomatic with a local reaction, lethargy, vomiting or hyperactivity. Incorrect dose administration was the largest cause of cases; 102 cases (28% of cases) were caused by this mechanism.

Papers not in English

a) Bruhn C. Diseases of the gastrointestinal tract and the skin in children - Part 7. Dtsch Apoth Ztg. September 13, 2007, 66-76
b) Sofo L et al. SELG-simeticone vs standard preparation in patients undergoing an endoscopic examination of large bowel. G Ital Endosc Dig. May 29, 1995, 37-42
c) Gaburro D, Burlina A. Management of acute infectious diarrhea in childhood. Riv Ital Pediatr. December 1, 1985, 122-7
d) Kark W, Krebs-Richter H, Hotz J. Improving the effect of orthograde colonic lavage with golytely solution by adding dimethicone. Z Gastroenterol. 1995 Jan;33(1):20-3
e) Friis H. Dimethicone in lactulose-induced dyspepsia. Effect on H2 production and Symptoms. Ugeskr Laeger. 1993 Oct 18;155(42):3378-80

Assessor's comment:

These papers have not been assessed at this stage. **The MA holder is requested to provide English translations of these papers for assessment.**

Papers that do not focus on the use of simeticone for the approved indications in children

a) Lesperance MM. A pediatric otolaryngologist learns to diagnose acute otitis media. Arch Otolaryngol Head Neck Surg. August 1, 2007, 745-6
b) Connor F. Gastrointestinal complications of fundoplication. Curr Gastroenterol Rep. June 1, 2005, 219-26
c) Orenstein SR et al. Nizatidine for the treatment of pediatric gastroesophageal reflux symptoms: An open-label, multiple-dose, randomized, multicenter clinical trial in 210 children. Clin Ther. April 1, 2005, 472-83
d) Ota FS, Abramo TJ, Maxson RT. Ominous findings in toddlers with increasing abdominal girth: Two unusual cases and a review of the clinical evaluation. Ann Emerg Med. May 1, 2005, 517-23
e) Perez A, Scribano PV, Perry H. An intentional opiate intoxication of an infant: When medical toxicology and child maltreatment services merge. Pediatr Emerg Care. November 1, 2004, 769-72
f) Spiro DM et al. Association between antibiotic use and primary idiopathic intussusception. Arch Pediatr Adolesc Med. January 1, 2003, 54-9
g) Ball R et al. Stevens-Johnson syndrome and toxic epidermal necrolysis after vaccination: Reports to the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J. March 6, 2001, 219-23
h) Bartel DR et al. Sclerodermalike esophageal disease in children of mothers with silicone breast implants. J Am Med Assoc. September 20, 1994, 767-70
i) Armstrong KL, Fraser DKB, Faoagali JL. Gastrointestinal bleeding with influenza virus. Med J Aust. March 11, 1991, 180-2)
j) Tsou VM et al. Multicenter, randomized, double-blind study comparing 20 and 40 mg of pantoprazole for symptom relief in adolescents (12 to 16 years of age) with gastroesophageal reflux disease (GERD). Clin Pediatr (Phila). 2006 Oct;45(8):741-9
k) Yang JC et al. The role of gastric acid and Helicobacter pylori in the natural course of duodenal ulcer. J Microbiol Immunol Infect. 1999 Sep;32(3):155-62
l) Corazziari E et al. Small volume isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in treatment of chronic nonorganic constipation. Dig Dis Sci. 1996 Aug;41(8):1636-42
m) Sherbaniuk RW et al. Comparative study of cimetidine and Mylanta II in the 6-week treatment of gastric ulcer. J Clin Gastroenterol. 1985 Jun;7(3):211-5
n) Hodgkinson R et al. Comparison of cimetidine (Tagamet) with antacid for safety and effectiveness in reducing gastric acidity before elective cesarean section. Anesthesiology. 1983 Aug;59(2):86-90
o) Korman MG et al. Influence of smoking on healing rate of duodenal ulcer in response to cimetidine or high-dose antacid. Gastroenterology. 1981 Jun;80(6):1451-3
p) Hanauer SB et al. Randomized, double-blind, placebo-controlled clinical trial of loperamide plus simethicone versus loperamide alone and simethicone alone in the treatment of acute diarrhea with gas-related abdominal discomfort. Curr Med Res Opin. 2007 May;23(5):1033-43

q) Simón A et al. The use of gastric ultrasonography in the evaluation of a new antiflatulent preparation in human volunteers. Methods Find Exp Clin Pharmacol. 1985 Jul;7(7):393-8
r) Albert J et al. Simethicone for small bowel preparation for capsule endoscopy: a systematic, single-blinded, controlled study. Gastrointest Endosc. 2004 Apr;59(4):487-91
s) Brouwers JR et al. A controlled trial of senna preparations and other laxatives used for bowel cleansing prior to radiological examination. Pharmacology. 1980;20 Suppl 1:58-64
t) Bowring AR, Mackay D, Taylor FR. The treatment of napkin dermatitis: a double-blind comparison of two steroid-antibiotic combinations. Pharmatherapeutica. 1984;3(9):613-7
u) Almeyda JJ et al. "Timodine" cream in the treatment of flexural dermatoses and napkin rash. Practitioner
v) de la Portilla F et al. Improved quality of anorectal endoluminal ultrasonography using emulsion of dimethicone. Dis Colon Rectum. 2003 Oct;46(10):1436-7

Assessor's comment:

Papers (a) to (m) mention simeticone in passing only, usually as an incidental concomitant medication or as an alternative treatment option mentioned in the introduction or discussion. These references do not provide any data or further information regarding simeticone's use in children for the approved indications.

Papers (n) to (r) are studies of simeticone use in adults only.

Paper (s) is a study of senna and other laxatives for bowel cleansing prior to radiological examination. In the results section of this paper, it is mentioned that a pilot study was undertaken during the course of the trial where simeticone was added to two different sennoside treatments. The pilot study was conducted as both sennoside treatments were noted to produce a high incidence of gaseous content in both groups. The addition of simeticone did not result in a reduction of gas content. No further details of the pilot study are provided in this paper.

Papers (t) and (u) are studies of treatments in napkin rash. Both studies assess the use of a cream, containing nystatin, hydrocortisone, dimeticone and benzalkonium chloride, for the treatment of this condition. This indication falls outside the scope of this work sharing procedure and will not be assessed further. No adverse events due to this combination drug were reported in either paper.

Paper (v) is a study of the use of degassed water when conducting anorectal endoluminal ultrasound and whether this method reduced the presence of air artefacts on the scan. Water was degassed using dimethicone and was instilled in the condom surrounding the ultrasound probe following insertion in the rectum. This study was performed in 42 subjects aged 17 to 72 years. As this indication for use of dimethicone falls outside the scope of this work sharing procedure it will not be assessed further in this report. No comment on adverse events was made in this paper.
These papers do not add any further understanding of the role of simeticone for the treatment of infantile colic or in bowel preparation, nor do they provide data that assists in reaching any conclusion on the safety of simeticone use in children.

3. Discussion on clinical aspects and conclusion

Efficacy

The NICE Clinical Knowledge Summary on the treatment of Infantile Colic (last revised in November 2014) states that a one-week trial of simeticone drops should be considered only "if

parents feel unable to cope despite advice and reassurance". Some simeticone products are indicated for use in this condition. The papers discussed in this report suggest that simeticone may not provide any benefit in the treatment of infantile colic, but may have a role in bowel preparation and the relief of symptoms of aerophagia and abdominal discomfort following inhalational anaesthesia. There are, however, significant limitations to the efficacy data presented in this report. It is therefore not possible to draw any conclusion on the efficacy, or otherwise, of simeticone in the treatment of infantile colic or for use in other indications based on the data presented in this report.

Safety

It is not possible to reach any conclusion on the safety of simeticone from the data presented here as little data regarding safety has been provided in the submitted papers. It is noted that the retrospective study of the epidemiology of ingestion events in 358 infants included seven cases of unintentional overdose involving simeticone. Further information on safety in general, and on unintentional overdose in particular, are important in the safety assessment for simeticone use in children.

A search of the MHRA pharmacovigilance database, which includes spontaneous reports from healthcare professionals, members of the public and pharmaceutical companies and literature references was conducted on 14th July 2016.

A total of 29 spontaneous suspected ADR reports relating to simeticone-containing products used orally in children aged less than 18 years old have been received in the UK since the start of records in 01/07/1963 until 14/07/2016 Of these reports, 26 reports were assessed as being related to simeticone use. 24 reports were of reactions occurring in children aged less than 1 year. Two cases of diarrhoea occurred in children aged 3 and 9 years of age. A summary of all reactions recorded is given in the following table.

Type of ADR reported	Number of cases reported	Other drugs taken in addition to SImeticone	Rechallenge data
Diarrhoea	5	Aluminium hydroxide, magnesium, dimeticone and didanosine in one	Positive to rechallenge with simeticone in a patient

		case.	taking no other medications.
Diarrhoea plus severe dehydration	1	None recorded.	Unknown.
Choking	4	None recorded.	Unknown.
Choking and Dyspnoea	1	None recorded.	Unknown.
Rash	2	Aluminium hydroxide and magnesium hydroxide in one case.	Unknown.
Dyspnoea	2	Vitamin K in one case.	Unknown.
Constipation and flatus	2	Alginic acid, aluminium hydroxide, magnesium trisilicate and sodium bicarbonate in one case.	Unknown.
Hypotonia	1	None recorded.	Unknown.
Bone marrow failure, Rash and Seizure	1	Pipenzolate	Unknown.
Sudden Infant Death	1	Pipenzolate	Unknown.
Abdominal distension	1	None recorded.	Unknown.
Apnoea	1	None recorded.	Unknown.
Dry skin/ eczema	1	None recorded.	Positive to rechallenge with simeticone in this patient
Cough	1	None recorded.	Unknown.
Drug dependence	1	None recorded.	Unknown.
Selective eating	1	Pipenzolate	Unknown.

V. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 70

The efficacy data presented have significant limitations that mean it is not possible to draw any conclusions on the efficacy, or otherwise, of simeticone for use in any paediatric indication. The rapporteur therefore concludes that based on the data submitted for assessment under this Article 45 procedure, no changes are deemed necessary in the approved paediatric indications.

It is not possible to reach any conclusion on the safety of simeticone based on the published articles presented here as little data regarding safety have been provided in the submitted papers. Further information on safety in general, and on unintentional overdose in particular, are important in the safety assessment for simeticone use in children.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

The submitted studies do not provide sufficient information to draw conclusions regarding potential adverse events specific to the paediatric population.

- The MAH is requested to supply data of all paediatric adverse events from their pharmacovigilance database. The MAH must compare all adverse events in each paediatric age group (i.e. children <1 year, aged 1 to <6 years, aged 6 to <12 years and aged 12 to <18 years) by frequency and severity with those observed in adults, in accordance with SmPC guidelines of September 2009. The applicant must also provide data by age group regarding unintentional and intentional overdose events and any factors that contributed to such events.

- The MAH must provide English translations of the five papers from the line listing that are not available in English in order that these documents may be assessed.

VII. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

In response to the rapporteur's request for supplementary information, the MAH provided data on paediatric adverse events from their pharmacovigilance database and the five papers from the line listing with their English translations.

1. Data on paediatric adverse events from the MAH's pharmacovigilance database
There are 12 cases with simeticone-containing medicinal products as suspect, or co-suspect drugs found in the MAH's safety database.

- Ten cases are reports of adverse reactions that occurred in adults.
- One case occurred in a 1.5-year old child. It was a non-serious case of a lack of efficacy from Finland received in 2004.
- In one non-serious case from the US the patient's age was not provided. The event was reported by the patient. The suspect drug was not a MAH's product and it was a fixed combination product containing simeticone.

Therefore, there were 0 cases in a group of <1 year, 1 case in a group of 1 to 6 years, 0 cases in a group of 6-12 years and 0 cases in a group of 12-18 years; 10 cases occurred in adults and in one case the patient's age was not provided.

The MAH stated that there were no cases of overdose.

Assessor's comment:

The MAH provided very limited information on adverse events in children based on their pharmacovigilance database; only one case of lack of efficacy in a 1.5 year old child was mentioned.

Based on these data, the rapporteur cannot draw conclusions regarding potential adverse events specific to the paediatric population.

2. English translations of the five papers previously not available in English

Translations of the following papers were provided by the MAH, with a brief evaluation of the data:

i) Bruhn C. Diseases of the gastrointestinal tract and the skin in children - Part 7. Dtsch Apoth Ztg. September 13, 2007, 66-76

The author presents an overview of disorders related to gastrointestinal system and skin in children and presents medications and non-plarmaceutical methods usually used to treat them. In this context, simeticone suspension is described as an anti-foaming agent authorised for use in children from the age of 1 week, as a first choice treatment in the case of infantile colic. The data presented by the author are not based on any scientific sources (i.e. no references to published literature are provided). In addition, no specific data on either efficacy or safety are presented in the article. The MAH concludes that the data presented in this paper are irrelevant to this work sharing procedure.

ii) Sofo L et al. SELG-simeticone vs standard preparation in patients undergoing an endoscopic examination of large bowel. G Ital Endosc Dig. May 29, 1995, 37-42

Efficacy (in terms of bowel cleansing, presence of bubbles and haziness of the image) and patient tolerance (occurrence of nausea, abdominal fullness and bloating, sleep loss) of the lavage solution with polyethylene glycol plus simethicone compared with a standard preparation (low residue diet, magnesium sulphate and senna) was assessed in a prospective randomized trial. Overall the tolerance was favourable to the polyethylene glycol plus simethicone solution. The objective parameters considered: cleansing, bubbles and sharpness of the image, the results were significantly in favour of the lavage solution preparation, with a subsequent improvement of the examination conditions.
The MAH considers that, as this is a combination preparation, a real contribution of simethicone on the obtained results cannot be distinguished.

iii) Gaburro D, Burlina A. Management of acute infectious diarrhoea in childhood. Riv Ital Pediatr. December 1, 1985, 122-7

The article focuses on treatment of acute infectious diarrhoea in childhood. Among methods and medicines used to deal with infectious diarrhoea, simeticone is mentioned as a nonspecific side-therapy of acute infectious enteritis. Simeticone belongs to the group of medicines which impact intestinal motility and effect in decreased hyper-mobility and intestinal spasms. Authors indicate that simeticone is not recommended in infectious diarrhoea, especially in childhood. In salmonellosis and shigellosis it can aggravate the infection, whereas inhibition of intestinal secretions is questionable. No discussion on the use of simeticone in infectious diarrhoea is

provided by the authors. No information on adverse reactions related to simeticone use is provided by the authors.

iv) Kark W, Krebs-Richter H, Hotz J. Improving the effect of orthograde colonic lavage with golytely solution by adding dimethicone. Z Gastroenterol. 1995 Jan;33(1):20-3

The authors conducted a prospective, randomised, placebo controlled and double blind study which investigated the efficacy of adding dimethicone during the orthograde colonic lavage with a sodium sulfate-based polyethylene glycol solution as part of the pre-colonoscopy preparation procedure. The study included a total of 152 patients (treatment group-78 patients, placebo group-74 patients, 96 females and 56 males, median age: 53 years, age range:16-85 years). The assessment was performed for the individual intestinal sections: sigmoid colon, descending colon, transverse colon, and ascending colon with cecum, based on criteria such as foam formation and faecal contamination. On the afternoon before the colonoscopy, patients received 3 litres of the lavage solution. Additionally, a total of 60ml of dimethicone or 60 ml of a placebo was administered and the patients received 30ml prior to the rinsing procedure and 30ml after taking 1.5l of 3l of the lavage solution. Patients were instructed to drink the lavage solution after having a light midday meal, within 4 hours whenever possible, before the date of the examination.
Significant improvement in the efficacy of colon endoscopy and shorter duration of the colonoscopy procedure was found in the dimethicone group when compared to the placebo group ($p<0.05$).
No side effects were observed. The authors conclude that the additional administration of dimethicone to patients undergoing orthograde colonic lavage with specific sodium based polyethylene glycol solution helps to ensure better preparation and assessment of the mucous membrane as well as facilitating the shorter duration of the colonoscopy procedure.

v) Friis H. Dimethicone in lactulose-induced dyspepsia. Effect on H2 production and Symptoms. Ugeskr Laeger. 1993 Oct 18;155(42):3378-80

Effects of dimethicone on H2 production and symptoms in lactulose induced dyspepsia were tested in a randomised, double blind, cross-over study on 10 healthy volunteers. There was no clinically relevant effect of simethicone on symptoms or intestinal gas production caused by carbohydrate malabsorption.

Assessor's comment:

Paper i) only briefly mentions simeticone as a first choice treatment for infantile colic, without any reference to studies or adverse events in the paediatric population.

Paper ii) compares 2 preparations in patients undergoing colonoscopy. The study included patients aged between 8 and 80 years (N=113, mean age 56 years, median 60 years). A standard preparation is compared to the combination of polyethylene glycol (PEG) plus simeticone. The use of the alternative combination preparation resulted in less adverse events, allowed a better visualization of the rectal-colonic mucosa and a greater number of examinations carried out. The assessor agrees with the MAH that the relative contribution of simeticone on the effects and adverse events observed in the study cannot be determined as a combination preparation was used, and not simeticone alone. In addition, it is not clear how relevant this paper is to children as it is not mentioned how many children were enrolled in the study.

Simeticone is not one of the drugs routinely used or recommended for bowel preparation before colonoscopy in children.

Paper iii) only mentions simeticone in a table of “antidiarrheal preparations” which are in general not recommended for acute infectious diarrhoea, especially in children. This paper has not provided any useful information regarding simeticone’s licensed paediatric indications or adverse events in children.

Paper iv) describes a randomised, placebo controlled, double blind study which investigated the efficacy of adding dimethicone during the orthograde colonic lavage with a specific solution as part of the pre-colonoscopy preparation procedure. The study provides some evidence that the addition of simeticone in the colonic lavage resulted in an improved colonoscopy in terms of duration, foam formation and faecal contamination. However, it is not clear how relevant the study is to the paediatric population as the number of patients between 16-18 years is not mentioned.

Paper v) presents a randomized, double-blind, cross-over study in ten healthy volunteers (18-34 years) who were given 30 g of lactulose and 600 mg of simethicone or placebo. This sufficiently large dose of lactulose to produce gastrointestinal symptoms was given to the volunteers, end-expiratory breath samples were collected and analyzed for H2, and gastrointestinal symptoms were registered. There were no differences in biochemical parameters or symptom score between simethicone and placebo. The study did not include children and therefore is not relevant to this work sharing procedure.

The papers mentioned above do not provide any additional information regarding simeticone’s use in children for the approved indications or regarding its safety in the paediatric population.

VIII. RAPPORTEUR’S OVERALL CONCLUSION AND RECOMMENDATION

Simeticone products available across the EU are indicated in children for the symptomatic relief of dyspepsia, heartburn, flatulence, gripping pain and infantile colic.

The MAH submitted published articles relating to the use of simeticone in infantile colic which is a licensed indication and other non-licensed uses of the drug such as bowel preparation, aerophagia, and abdominal discomfort following inhalational anaesthesia.

Based on the data submitted as part of this work sharing procedure under Article 45, the rapporteur concludes that no changes are needed in the approved paediatric indications and in the posology for children.

The MAH reviewed pharmacovigilance data and published papers and provided limited information on adverse events in children following simeticone use. A search of the MHRA pharmacovigilance database was also conducted, covering the period 01/07/1963 until 14/07/2016 which yielded a total of 29 spontaneous suspected ADR reports relating to simeticone-containing products used orally in children. No new safety data that would warrant regulatory action were identified by the rapporteur.

The rapporteur reviewed the data submitted by the MAH and concludes that simeticone's benefit:risk ratio has not changed following this procedure.

IX. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Active Substance(s)	Name of the medicinal product	Strength	Pharmaceutical form
Simeticone	Disflatyl	40 mg/ml	Oral drops