VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acute diarrhoea is very common and often a symptom of diseases or other medical
Acute diarrhoea occurs in all populations and age groups. A decrease in consistency
liquid) and an increase in frequency of bowel movements to >3 stools per day has
used as a definition of diarrhoea for epidemiological investigations. Diarrhoea is an a
normal bowel movement characterized by an increase in the water content, volume, o
of stools. Intestinal water balance results from a complex regulation involving in
mediators, hormones, neuropeptides, integrity of the intestinal wall, efficiency of the
system and of the enteric nervous system [Guerrant et al. (2001) in **Baldi** et al. (2009)]
Globally, there are approximately 1.5 to 2 billion cases of diarrhoea yearly [WH
Farthing et al. (2010) in **McClarren** et al (2011)]. Internationally, in the year 2000, dia
responsible for the deaths of 1.5 to 2 million children who were under the age of
resource-poor countries, diarrhoea is second only to pneumonia in lethality in this
Population groups at particular risk for significant morbidity and mortality are the v
the elderly, the undernourished, and the immunocompromised. Those who live in ar
safe food and water supplies, good hygiene practices, basic medical care, and adequa
are especially vulnerable.

VI.2.2 Summary of treatment benefits

Loperamide hydrochloride – simeticone is available in pharmacies and not the only option for the treatment of acute diarrhoea. Other drugs are also available, also over-the-counter (OTC) products.

When diarrhoea is severe, efforts to replace fluid losses should be of highest priority; rapid deterioration can progress to death in a matter of hours if treatment is delayed. Young children, the elderly, the immunocompromised, and the malnourished are particularly vulnerable.
Fortunately, most patients with diarrhoea are able to tolerate oral fluids. Breastfed infants should continue to nurse [Weinberg et al. (2011) in **McClarren** et al (2011)]. In many areas, the World Health Organization (WHO) Oral Rehydration Solution (ORS), is supplied in packets to be mixed with clean water. A variety of recipes for "homemade" ORS are available on Internet sites.
Except in rare circumstances, a regular diet is encouraged after the initial correction of dehydration. Although the BRAT (bananas, rice, applesauce, and toast) diet, has been widely used, it is not advised due to nutritional inadequacies. Early re-feeding was shown to decrease stool volume during the recovery period.
In adults, symptoms of infectious diarrhoea can often be significantly improved by the administration of diphenoxylate (combined with atropine in the formulation of Lomotil). This is an antimotility agent and should not be given in the presence of fever, severe pain, or dysenteric stools. Administration to children and the elderly is contraindicated. Central nervous system depression, bloating, constipation, and toxic megacolon have been observed with the use of antimotility agents. Although antibiotics and antimotility agents are sometimes prescribed concurrently, this practice has unknown effectiveness.
Bismuth subsalicylate (Pepto-Bismol and Kaopectate) has been in use for more than a century and is thought to have a multifactorial mechanism of action.
Racecadotril is a purely antisecretory drug that has been used successfully in both children and adults. The incidence of adverse side effects is similar to placebo. It has been in widespread use internationally for a number of years but cannot be purchased in the United States.
Probiotic use has received attention as both an effective prophylaxis and treatment modality for infectious diarrhoea. Preliminary studies support the hypothesis that both the type and quantity of ingested probiotics are factors in the prevention and treatment of some types of infectious diarrhoea.

VI.2.3 Unknowns relating to treatment benefits

Loperamide hydrochloride – simeticone tablets are indicated for the symptomatic treatment of acute diarrhoea in adults and adolescents over 12 years when acute diarrhoea is associated with gas-related abdominal discomfort including bloating, cramping or flatulence. Loperamide hydrochloride – simeticone was not studied and is not indicated for use in children younger than 12 years of age. This product has been in use for many years and the safety profile of the active ingredient is well established, therefore almost all different populations are exposed and the effects of loperamide hydrochloride – simeticone on these different populations are known.

VI.2.4 Summary of safety concerns

Loperamide hydrochloride – simeticone belongs to a group of medicines called antipropulsive antidiarrhoeals, which are medicines against diarrhoea. It is used for the symptomatic treatment of acute diarrhoea when it is associated with gas-related abdominal discomfort including bloating, cramping or flatulence (passing gas).

Loperamide hydrochloride – simeticone is a medicine, which is available in pharmacies and has been on the market for a considerable period of time. It is considered a safe product when used for the above indication. Nonetheless, the use of this product can carry some risks, which people should be aware of before taking the product (see the table below). Range numbers given below regarding the occurrence of the reactions refer to a percentage of the patients taking loperamide hydrochloride – simeticone.

Summary of safety concerns – important identified risks

Risk	**What is known**	**Preventability**
Hypersensitivity	Hypersensitivity reactions can occur with and without previous exposure to loperamide hydrochloride – simeticone. The frequency of the reactions is unknown (cannot be estimated). The reactions can be mild but also very serious. Treatment for all these reactions is available and will result in a quick recovery of the patient.	When it is proven that the allergic/hypersensitivity reaction is due to loperamide hydrochloride – simeticone or one of the excipients, it can be easily prevented by not taken the drug again. A previous allergic reaction to loperamide hydrochloride – simeticone is also a contraindication for the use of loperamide hydrochloride – simeticone so this patient population will then be excluded from the use of loperamide hydrochloride – simeticone.
Ileus, megacolon and toxic megacolon	Several warnings and interactions are known with the use of loperamide hydrochloride – simeticone and intestinal safety. Loperamide hydrochloride – simeticone tablets should not be used when inhibition of peristalsis is to be avoided due to the possible risk of significant sequelae including ileus, megacolon and toxic megacolon. It must be discontinued promptly if constipation, ileus or abdominal distension develop. Patients with AIDS treated with loperamide hydrochloride – simeticone tablets for diarrhoea should have therapy stopped at the earliest signs of abdominal distension. There have been isolated reports of obstipation with an increased risk for toxic megacolon in AIDS patients with infectious colitis from both viral and bacterial pathogens treated with loperamide hydrochloride Known adverse events with the	Loperamide-simeticone must be stopped promptly if constipation, ileus or abdominal distension develop. Patients with AIDS treated with loperamide hydrochloride – simeticone tablets for diarrhoea should have therapy stopped at the earliest signs of abdominal distension.

Risk	What is known	Preventability
	use of loperamide hydrochloride – simeticone are megacolon including toxic megacolon, ileus (frequency is unknown).	

Summary of safety concerns – important potential risks

Risk	What is known
Exposure during pregnancy and breast feeding	A limited amount of data from the use of loperamide in pregnant women is available. In one of two epidemiological studies the use of loperamide during early pregnancy suggested a possible moderate increased risk for hypospadias (birth defect of the urethra of the male), however, an increased risk for major malformations could not be identified [**Källén** et al (2008)]. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. If possible the use of loperamide hydrochloride – simeticone should be avoided during the first trimester of pregnancy, however, it may be used during the second and third trimester of pregnancy. Only very small amounts of loperamide hydrochloride may appear in human breast milk. Therefore, loperamide hydrochloride – simeticone may be used during breast feeding when dietary measures are insufficient and a drug-induced inhibition of intestinal motility is indicated.
Fertility	Only high doses of loperamide hydrochloride affected female fertility in non-clinical studies. In reproduction studies, very high doses (40 mg/kg/day - 240 times the maximum human use level) loperamide impaired fertility and foetal survival in association with maternal toxicity in rats. Lower doses had no effects on maternal or foetal health and did not affect peri- and post-natal development.

Summary of safety concerns – important missing information

Risk	What is known
Exposure in children younger than 12 years old	The use of loperamide hydrochloride – simeticone is not indicated for treatment in children younger than 12 years old. Loperamide hydrochloride – simeticone should therefore not be used in children younger than 12 years.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Details of the routine risk minimisation measures are provided in the product information.

Routine pharmacovigilance practice and appropriate product labeling are considered to be sufficient. Therefore, no additional risk minimisation measures are planned for any of the important identified risks, important potential risks, or missing information. No post-authorisation development plan is required.

VI.2.6 Planned post-authorisation development plan

No post-authorisation studies are planned and therefore this section is not applicable.

VI.2.7 Summary of changes to the risk management plan

Not applicable, since this is the first RMP of loperamide hydrochloride – simeticone.