

Duphalac Fruit 667 mg/ml

11.2.2014, Version 1.0

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Constipation (infrequent bowel movements, hard and dry stools)

Constipation refers to bowel movements that are infrequent (less than three times per week) or hard to pass. It is characterized by painful defecation and straining. Constipation is a common problem that affects up to 1 in 5 people and occurs in all ages from newborns to elderly people, however it is more frequent in the elderly. Constipation is more common in women – particularly during pregnancy or after childbirth – and non-whites. Severe constipation may lead to failure to pass stool or gas and fecal impaction. Severe constipation may progress to bowel obstruction with potential life-threatening consequences.

There are several factors that contribute to constipation; including not drinking enough fluids or not eating enough fiber, bowel disorders, depression or eating disorders. It may also be related to an underlying medical condition or a side-effect of certain medicines.

The first approach to treat constipation is to start with lifestyle and diet changes. Following that, medications may be started to increase bowel movements.

Where a soft stool is considered of medical benefit if hemorrhoids (piles) are present and after anal surgery or surgery to the lower bowel)

Hemorrhoids (piles) are swellings that develop from the back passage. They originate from blood vessel structures, which – in their natural state – help with stool control. Those structures become piles when swollen or inflamed. Piles affect millions of people around the world and the movement of hard stools may result in worsening the problem. The exact frequency of this condition is unknown as patients have the tendency to treat themselves rather than get medical advice, however it is estimated to be 1 in 20 people. It is more frequent in white people in rural areas, and pregnant women due to changes to their body. Swelling of blood vessels around the anus is more common in young to middle-aged adults.

Certain situations can increase the chance of developing piles, these include constipation, diets which are low in fiber, age, pregnancy and strain from painful or hard bowel movements.

Drinking more fluids and eating more fiber can improve symptoms. However, where this is not possible medications can help soften stools.

Hepatic encephalopathy – occurrence of confusion, tremor and decreased level of consciousness including coma as a result of liver failure

Hepatic encephalopathy is a symptom of late-stage liver disease (liver cirrhosis). Information on the frequency of hepatic encephalopathy is limited. However it is thought that underlying

forms can be seen in 4 out of 5 people with more advanced liver scarring. It can occur at any age, however it is most common in people in their 50's and 60's, with both men and women being equally affected. There are no racial or genetic factors that influence this disease.

Hepatic encephalopathy is thought to be caused by accumulation of toxic substances that are normally removed by the liver. Increased levels of ammonia are usually associated with the disease. Factors that may contribute include alcohol or substance abuse, dehydration, increased protein in the diet, an imbalance of electrolytes as well as gastrointestinal bleeding (which are also common complication in late-stage liver disease) and infections.

Supportive care should be initiated and treatment with medications that will reduce the production of ammonia.

VI.2.2 Summary of Treatment Benefits

Constipation/where a soft stool is considered of medical benefit

Lactulose has consistently shown to be a beneficial product for the treatment of constipation and where a soft stool is considered of medical benefit. It has been marketed for almost 50 years. Over decades of lactulose use, a large number of studies have been conducted worldwide, consistently confirming the safety and efficacy of lactulose in these indications.

Hepatic encephalopathy – occurrence of confusion, tremor and decreased level of consciousness including coma as a result of liver failure

A large number of studies in hepatic encephalopathy have demonstrated the efficacy of lactulose. Lactulose is considered the mainstay therapy in the treatment of this symptom of liver disease. Most of the primary interventions for this indication are directed towards reducing the production of ammonia by the gut flora. Lactulose has proven to reduce synthesis and absorption of ammonia significantly. Few alternative treatments are available, the efficacy of which is often assessed on top of treatment with lactulose.

Lactulose makes the stool softer and easier to pass, basically by drawing water into the bowel. In addition it has a couple of other beneficial effects, like decreasing ammonia blood levels by – among other mechanisms – leading in this respect to a more favorable balance of the intestinal flora. Lactulose is poorly absorbed into the body and no clinically relevant drug-drug interactions have been described. In light of its well-established positive safety profile, it can be used in all age groups, including children, the elderly and pregnant women. Over the decades a large number of studies have been performed that consistently show the benefits of lactulose and it is now known throughout the medical community and the general public that it has a favorable safety profile.

Lactulose has been marketed for almost 50 years, and it has been estimated from sales information that more than 645 million patients have been exposed to lactulose: It can be stated that lactulose is a safe and well tolerated product when used as indicated.

VI.2.3 Unknowns Relating to Treatment Benefits

The safety and efficacy in children (newborn to 18 years of age) with hepatic encephalopathy have not been established due to the lack of controlled clinical and post-marketing experience. For this reason the use of lactulose in children under the age of 18 years with hepatic encephalopathy has been identified as missing information.

VI.2.4 Summary of Safety Concerns

There are three important identified safety risks associated with lactulose.

| Risk | What Is Known | Preventability |
|---------------------------------------|--|---|
| Electrolyte imbalance due to diarrhea | A small number of people (may affect up to 1 in 100 people) may experience an electrolyte imbalance due to diarrhea while taking lactulose. This can occur especially if high doses are taken for an extended period of time. Chronic use of unadjusted dosages (maintenance dose is recommended to be adjusted to achieve 2-3 soft stools per day) or misuse can also lead to diarrhea and disturbance of electrolyte balance. Patients with predisposing factors to electrolyte imbalance (among others, diuretic treatment, renal insufficiency or renal failure, bulimia or anorexia nervosa) may be at an increased risk of electrolyte imbalance if they experience gastrointestinal disorders such as diarrhea and vomiting as a result of unadjusted doses or misuse of lactulose. | Yes, by monitoring for early symptoms, not exceeding the recommended dose and following the recommendations in the product information: Chronic use of unadjusted doses can lead to diarrhea and disturbance of the electrolyte balance. After a few days with the appropriate starting dosage, posology should therefore be adjusted according to the patients' individual needs and a lower daily maintenance dosage is to be targeted based upon treatment response. During treatment with laxatives it is recommended to drink sufficient amounts of fluids during the day in order to guarantee the optimal success of treatment. |

| Table 20. Important Identified Risks | | |
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| Risk | What Is Known | Preventability |
| Use in patients with a severe genetic disorder where you cannot digest galactose (galactosemia) | This is a rare genetic disorder where the patient cannot digest galactose and can result in life-threatening complications. Lactose and galactose are to be eliminated from the diet. Lactulose may contain small amounts of lactose and galactose and due to the seriousness of the disease, lactulose must not be given to patients suffering from galactosemia. | Product information clearly states that this specific population must not take lactulose. |
| Use in patients with a blockage in their gastrointestinal tract, digestive perforation or at risk of digestive perforation | The risk of complications of blockage and perforation in the gastrointestinal tract is increased by the use of laxatives, due to an increase in intestinal movements and the volume of bowel contents. Furthermore, usage of laxatives in patients at risk might contribute to final perforation. There are several conditions which might predispose to gastrointestinal perforation. In any case, the decision on whether or not a patient is at increased risk for perforation is at the discretion of the treating physician. The decision would be dependent on severity and stage of the predisposing factors. | Product information clearly states that patients with these conditions must not take lactulose. Furthermore recommendation is given to first (before taking lactulose) consult a doctor in case patient is suffering from unexplained stomach ache as (severe) pain is one of the leading symptoms in case of gastrointestinal perforation or obstruction as well as in conditions which might predispose to these. |

| Table 21. Missing information | |
|---|--|
| Risk | What Is Known |
| Use in children (newborn to 18 years of age) with hepatic encephalopathy) | Lactulose is indicated for the treatment of constipation independent of age, from newborns to the elderly. Lactulose is also indicated for the treatment of hepatic encephalopathy. The safety and efficacy in children (newborn to 18 years of age) with hepatic encephalopathy, have not been established. For this reason the use of lactulose in children under the age of 18 years with hepatic encephalopathy has been identified as missing information and no dosage recommendations are available. |

VI.2.5 Summary of Risk Minimization Measures by Safety Concern

All medicines have a CCDS which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimization measures.

Local SmPCs and the Package leaflet for lactulose are publically available.

This medicine has no additional risk minimization measures (that is there are no special conditions or restrictions for its safe and effective use in place).

VI.2.6 Planned Post-Authorization Development Plan

This section is not applicable. The safe and efficient use of lactulose is well-established in clinical practice and there are no pertinent gaps which must be addressed in dedicated patient studies. Thus no studies are currently planned or on-going with lactulose in order to further characterize its already well-established safe use or effectiveness in patients. There are no studies imposed as a condition of the Marketing Authorizations.

VI.2.7 Summary of Changes to the Risk Management Plan over Time

Not applicable.