Abbott Laboratories South Africa (Pty) Ltd	Submission Date: 30 November 2022
DUPHALAC	Approval Date: 30.01.2023
3,3g/5mL syrup	Implementation: 30.01.2023
Country Code: ZA	Reg No.: K/11.5/180

1.5.5.1 ANNOTATED PROFESSIONAL INFORMATION

PROPOSED CLEAN PROFESSIONAL INFORMATION

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

DUPHALAC 3,3 g/5 mL syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mL DUPHALAC contains lactulose (4-0-b-D-galactopyranosyl-D-fructofuranose) 3,3 g.

For the full list of excipients, see section 6 .1.

DUPHALAC contains residues from the route of production with known effect, see section 4.4.

3. PHARMACEUTICAL FORM

A clear, viscous liquid, colourless to pale brownish-yellow syrup.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Constipation

Particularly when associated with laxative habituation or for those patients in whom constipation presents a special problem, e.g. children, obstetric and post-surgical patients.

Portal systemic encephalopathy

Hepatic coma or precoma stages where hyperammonaemia is present.

Sign: _____

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4.2 Posology and method of administration

Posology

Constipation

Dosage can vary widely with the severity of the condition. A relatively large initial dose should be followed by a smaller maintenance dose after the first three days of treatment. Only one dose daily needs to be taken, preferably after breakfast.

Recommended dosages are as follows:

Usual starting dose

Adults: 30 mL (6 x 5 mL spoonfuls).

Children (6-14 years): 15 mL (3 x 5 mL spoonfuls).

Children (1-5 years): 10 mL (2 x 5 mL spoonfuls).

Infants: 5 mL (1 x 5 mL spoonful).

Maintenance dose

Adults: 15 – 30 mL (3 – 6 x 5 mL spoonfuls).

Children (6-14 years): 10 – 15 mL (2 – 3 x 5 mL spoonfuls).

Children (1-5 years): 5 – 10 mL (1 – 2 x 5 mL spoonfuls).

Infants: 2,5 – 5 mL (½ – 1 x 5 mL spoonful).

Portal systemic encephalopathy

Initial dose of 30 – 50 mL 3 times daily. Subsequently adjust the dose to produce two or three soft stools daily.

Sign: _____

4.3 Contraindications

Hypersensitivity to lactulose (see section 2).

Galactosaemia.

Gastrointestinal obstruction, perforation in the digestive organs or risk of this (for example, acute inflammatory diseases of the intestine, such as colitis ulcerosa, Crohn's disease).

4.4 Special warnings and precautions for use

It is advised that a doctor should be consulted in the case of:

- painful abdominal symptoms of unknown origin before the treatment is started;
- insufficient therapeutic effect after a few days.

DUPHALAC should be given with caution to patients with a lactose intolerance.

The usual dosage in constipation does normally not pose a problem for diabetics. The dosage used in the treatment of portal systemic encephalopathy is usually much higher and may need to be taken into consideration with diabetics.

Note should, however, be taken that DUPHALAC contains small amounts of lactose, galactose and fructose from the manufacturing process. Patients with rare hereditary galactose or fructose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take DUPHALAC. DUPHALAC contains residues of sulphite from the manufacturing process.

Patients with a gastro-cardiac syndrome (Roemheld syndrome) should use lactulose only after consulting a doctor. If symptoms such as meteorism or distension occur in these patients after

taking DUPHALAC, the dosage should be reduced, or treatment should be discontinued.

Chronic use of unregulated doses and abuse may lead to diarrhoea and disturbance of the electrolyte balance.

Paediatric population

Laxatives should only be used in children in exceptional cases and under medical supervision.

Caution should be exercised when giving DUPHALAC to babies and small children who have a rare autosomal recessive fructose intolerance.

It should be taken into account that the reflex that causes defecation may be disturbed during the treatment.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been carried out.

DUPHALAC may increase the potassium loss induced by other medicines (for example thiazides, corticosteroids and amphotericin B).

Concomitant use of cardiac glycosides may increase the effect of the glycosides due to potassium deficiency.

4.6 Fertility, pregnancy and lactation

Pregnancy

No effects are anticipated during pregnancy since the systemic exposure to lactulose is negligible.

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Lactation

No harmful effects on the health of the child during breastfeeding are anticipated, since the systemic exposure to lactulose is negligible.

Fertility

No effects are anticipated because the systemic exposure to lactulose is negligible.

4.7 Effects on ability to drive and use machines

DUPHALAC has no or a negligible effect on the ability to drive or use machines.

4.8 Undesirable effects

Although occasionally nausea and meteorism or flatulence have been reported on the high initial dosages used, these effects normally disappear when the maintenance dosage has been reached.

If the dosage given is higher than prescribed, abdominal pain and diarrhoea may occur. The dosage should then be reduced.

If high doses (normally only for portal systemic encephalopathy, PSE) are used for an extended period, the patient's electrolyte balance may be disturbed as a result of diarrhoea.

Immune system disorders

Not known: hypersensitivity

Gastrointestinal disorders

frequent: diarrhoea, flatulence, abdominal pain, nausea, vomiting

Sign: _____

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Common: flatulence, abdominal pain, nausea, vomiting

Skin and subcutaneous tissue disorders

Frequency unknown: rash, pruritus, urticaria, erythema

Investigations

Less frequent: disturbed electrolyte balance as a result of diarrhoea

Paediatric patients

The safety profile is expected to be the same in children as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of DUPHALAC is important. It allows continued monitoring of the benefit/risk balance of DUPHALAC. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8.

Symptoms: Diarrhoea and abdominal pain.

Treatment: Stop treatment with DUPHALAC or reduce the dose. Extreme fluid loss due to diarrhoea or vomiting may require correction of the disturbed electrolyte balance.

Sign: _____

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A. 11.5 Laxatives

Pharmacotherapeutic group: Osmotic laxatives

ATC code: A06AD11

Mechanism of action

In the colon lactulose is converted by the intestinal flora into low-molecular organic acids. These acids lead to a lowering of pH in the colonic lumen and via an osmotic effect to an increase of the volume of the colonic contents. These effects stimulate the peristalsis of the colon and normalise faecal consistency. The constipation is relieved, and the physiological rhythm of the colon is restored.

In portal systemic encephalopathy (PSE) lactulose causes a decrease in the ammonia content of the blood. The higher dosage used in this indication results in a lower pH in the colon. The growth of proteolytic bacteria is consequently inhibited, resulting in reduced production of ammonia and other toxins.

At this lower pH a high percentage of ammonia is also converted into ionised ammonia, which passes through the colon wall with difficulty. The ability of ammonia to be absorbed is consequently reduced. As a result of the lowered pH, ammonia additionally diffuses from the blood towards the colonic lumen. The effect is additionally reinforced by the generally accelerated passage time in the colon. Protein tolerance is increased by this change in ammonia metabolism. Within this context it is important to realise that hyperammonaemia alone cannot explain the

neuropsychiatric manifestations of PSE.

As a prebiotic substance, lactulose intensifies the growth of *Bifidobacterium* and *Lactobacillus*, while *Clostridium* and *Escherichia coli* may be suppressed. This may lead to alleviation of the constipation and, in this way, have a favourable effect on the patient's state of health.

5.2 Pharmacokinetic properties

Lactulose is poorly absorbed after oral administration, and it reaches the colon unchanged. There it is metabolised by the colonic bacterial flora. Metabolism is complete at doses up to 25 – 50 g or 40 – 75 mL; at higher doses, a proportion may be excreted unchanged.

5.3 Preclinical safety data

The results of acute, sub-chronic and chronic toxicity studies in various species of animals indicate very low toxicity. The effects observed appear to be related more to the effect of bulk in the gastrointestinal tract than to a more specific toxic activity. No adverse effects were found in reproduction and teratology experiments in rabbits, rats and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

DUPHALAC does not contain any added excipients.

6.2 Incompatibilities

Not applicable.

Sign: _____

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6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 ˚C.

6.5 Nature and contents of container

150 mL, 500 mL, 2,5 L and 5 L bottles.

Boxes of either 6, 10, 20 or 30 sachets containing 15 mL DUPHALAC.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

K/11.5/180

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 August 1979

Sign: _____

1.5.5.1 ANNOTATED PROFESSIONAL INFORMATION

10. DATE OF REVISION OF THE TEXT

30 January 2023

Sign: _____