Summary of Product Characteristics

Normapro

1. Name of the Medicinal Product

1.1 Product Name

Normapro

1.2 Strength

Lyophilized dry yeast of *Saccharomyces boulardii* 250 mg

(Corresponding to at least $2x10^{10}$ viable cells/g)

1.3 Pharmaceutical Dosage Form

Capsule, hard

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

2.2 Quantitative Declaration

Active substance
1 hard capsule contains:
250 mg dry yeast from S*accharomyces boulardii (Saccharomyces cerevisiae* HANSEN CBS 5926), corresponding to at least $2x10^{10}$ viable cells/g; lyophilised.

Other constituents with known effects: Lactose

For a full list of excipients, see section 6.1 'List of excipients'.

3. Pharmaceutical Form

Opaque white/white hard vegetable capsules with ochre to beige-grey coloured, granular powder

4. Clinical Particulars

4.1 Therapeutic indications

- Establish and maintain a well-functioning intestinal flora and an intestinal health. (Ref no. 1, page 159-160, no. 1.1; Ref no. 5, page 2207, no. 1.2)
- Treatment of acute diarrhea. (Ref no. 1, page 166, no. 1.3; Ref no. 5, page 2212, no. 1.4)

- Prevention and treatment of traveler's diarrhea. (Ref no. 5, page 2213, no. 1.5; Ref no. 6, page 235, no. 1.6)
- Prevention of antibiotic induced diarrhea. (Ref no. 1, page 163, no. 1.7; Ref no. 5, page 2208, no. 1.8)
- Treatment of *Clostridium difficile* diseases such as antibiotic associated colitis. (Ref no. 1, page 165, no. 1.9; Ref no. 5, page 2210, no. 1.10)
- In patient with *H.pylori* infection, along with standard triple therapy for increasing the eradication rates and decreasing overall therapy-related side effects, particularly diarrhea. (Ref no. 2, page 2, no. 1.11; Ref no. 5, page 2211, no. 1.12)
- Treatment of irritable bowel syndrome. (Ref no. 5, page 2214, no. 1.14)

4.2 Posology and method of administration

Posology

Adults: 1 capsule once or twice daily or as direct by physician. (Ref no. 1, page 166, no. 2.1; Ref no. 5, page 2212-2213, no. 2.2; Ref no. 6, page 236, no. 2.3)

Treatment of *H.pylori* symptoms with standard triple therapy:

Take 1 capsule 4 times daily for 2 weeks with standard triple therapy or as directed by physician. (Ref no. 2, page 7, no. 2.4; Ref no. 5, page 2216, no. 2.5)

Treatment of *Clostridium difficile* diseases such as antibiotic associated colitis:

Take 1 capsule 4 times daily for 4 weeks with standard therapy (vancomycin or metronidazole) or as directed by physician. (Ref no. 1, page 166, no. 2.6; Ref no. 5, page 2216, no. 2.5)

For prevention of traveler's diarrhea: 1 capsule once or twice daily or as direct by physician. Starting 5 days before departure and should be carried out consistently over the entire travel period. (Ref no. 5, page 2213, no. 2.7; Ref no. 6, page 236, no. 2.8)

Children less than 2 years: Should be used under medical supervision only (Ref no. 4, page 4, no. 2.9)

Children 2 years old and over: 1 capsule once or twice daily (Ref no. 4, page 4, no. 2.9; Ref no. 6, page 236, no. 2.10)

Direction of use for children: Take off the capsule shell and put the content of a capsule into water or juice around 5-10 ml. Do not mix with very hot (over 50°C) water.

Duration of use

If the symptoms persist longer than one week during the use of the medicinal product, a doctor or a pharmacist should be consulted. (Ref no. 4, page 4, no. 2.11)

Method of administration

Oral use

4.3 Contraindications: (Ref no. 3, page 2, no. 4.1; Ref no. 5, page 2216, no. 4.2; Ref no. 6, page 235, no. 4.3; Ref no. 8, page 1631, no. 4.4)

- Normapro should not be used in person with known hypersensitivity to yeast or any component in Normapro.
- Normapro contains lactose. Normapro should not be used in person with lactose intolerance.
- Due to the unpredictable risk of a systemic colonization with *Saccharomyces boulardii* patients with these diseases are contraindicated to use:
  - Patients with heavily impaired immune defense system (e.g. HIV-infections, Organ transplantation, Leukaemia, Malignant tumors, Radiotherapy, Chemotherapy, Long-term high-dose cortisone treatment).
  - Patients with central venous catheter.

4.4 Special warnings and precautions for use (Ref no. 6, page 236, no. 5.1)

Should consult the physician, in case of diarrhea last longer than 2 days of treatment, in case of fever or vomiting or in case of presence of blood or mucus in the stools. For diarrhea, especially in children, should use electrolytes together when dehydration.

4.5 Interaction with other medicinal products and other forms of interaction (Ref no. 3, page 2, no. 6.1)

Taking Normapro with medications for fungal infections can reduce the effectiveness of Normapro. Normapro can be taken with antibiotic drug if requires.

4.6 Fertility, pregnancy and lactation (Ref no. 3, page 2, no. 7.1; Ref no. 6, page 236, no. 7.2)

There is no sufficient safety data for the use of *Saccharomyces boulardii* during Pregnancy & Lactation. The use of *Saccharomyces boulardii* during pregnancy & lactation should be avoided.

No fertility data are available.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects (Ref no. 3, page 2, no. 8.1; Ref no. 6, page 235, no. 8.2)

May often cause flatulence.

4.9 Overdose

Have not been reported.

5. Pharmacological Properties

5.1 Pharmacodynamic properties (Ref no. 4, page 1, no. 3.4, Ref. no. 9-17)

Pharmacotherapeutic group: Dry yeast from cultures of the defined strain *Saccharomyces cerevisiae* HANSEN CBS 5926 (*Saccharomyces boulardii*) in viable form, group of microbial anti-diarrhoeal drugs

ATC Code: A07FA02

Probiotics like *Saccharomyces boulardii* is nonpathogenic microorganisms. It has been suggested that they improve host barrier function, produce competitive inhibition of pathogenic bacteria, and bolster immune function. It also secretes enzymatic proteins, including a protease that degrades *Clostridium difficile* toxins and a phosphatase that inactivates endotoxins such as the lipopolysaccharide produced by *E. coli.*

From the literature search, a protective mechanism can be derived from *Saccharomyces boulardii,* which has an effect on pathogenic micro-organisms causing diarrhoea. On the basis of the experimental data available, it can be assumed that various mechanisms for this effect are feasible, such as e.g. the binding of yeasts to bacteria and the inhibition of bacterial growth, effects on microbial metabolism, anti-secretory effects, effects on the mucosa, immunological and anti-inflammatory effects. This effect is also associated with the viability of the yeast cells.

In a randomised, placebo-controlled study for the treatment of acute diarrhoea in adults, 43 patients were treated with 3 x 200 mg *Saccharomyces boulardii* in the first 2 days and with 3 x 100 mg from days 3 to 7. 49 patients received a placebo. With regard to the frequency of stools passed, the average number of stools per 24 hours, stool quality and

further accompanying variables such as nausea, moderate results were shown in favour of verum.

In a multi-centre, non-controlled post-marketing study, good tolerability was achieved in patients with acute diarrhoea, who were treated with *Saccharomyces boulardii* over a period of 4 days. From 3026 patients, the data from 2911 patients could be evaluated; of these, 450 were children aged 1 to 5 years. Children between 1 and 5 years were given 3 x 150 mg, all other patients received 3 x 200 mg. 8 patients complained of stomach ache or flatulence.

Two published double-blind, randomised, placebo-controlled studies were carried out to demonstrate a preventive effect in travel diarrhoea. A total of 2247 adults took part in the evaluation. 1480 patients were treated with different doses of *Saccharomyces boulardii* (2 x 125 mg, 2 x 250 mg, 1000 mg). There was a significantly lower occurrence of diarrhoea in the *S. boulardii* groups in comparison to placebo. A dose of 250 mg per day was most frequently used. No clear dose dependency could be shown.

In a multicentre prospective clinical trial evaluating the efficacy and safety of *Saccharomyces boulardii* in preventing antibiotic-associated diarrhoea in patients receiving antibiotics for *H. pylori* eradication, patients with peptic ulcer disease or non-ulcer dyspepsia were enrolled to receive clarithromycin, amoxicillin and omeprazole for *H. pylori* eradication for 14 days. These patients were then randomized to receive either *S. boulardii* (2x250 mg twice daily) (treatment group) or no treatment (control group). Of the 389 patients that were enrolled, 376 completed the study. Within the treatment period, diarrhoea developed in the treatment group significantly lower than the control group. Besides, diarrhoea in the follow-up period developed in the treatment group lower than the control group. Overall diarrhoea rates throughout the whole study period were significantly higher in the control group than the treatment group. No significant difference was observed between the treatment and control groups in terms of adverse events. In conclusion, *S. boulardii* is an effective and safe treatment for the prevention of antibiotic-associated diarrhoea when given concomitantly to patients receiving *H. pylori* eradication.

Pseudomembranous colitis, an inflammation of the colonic mucosa, is most commonly caused by *C. difficile*, a gram-positive anaerobic spore-forming bacillus that is not part of

normal human flora. Antibiotic administration, particularly with broad-spectrum agents, can alter colonic microflora, resulting in overgrowth of *C. difficile*. Hospitalized patients are at greatest risk for *C difficile*. Once in the colon, pathogenic strains release toxins A and B which bind to receptors in the colonic mucosa, resulting in fluid secretion, inflammation, and mucosal damage.

In a double-blind, randomized, placebo-controlled, parallel-group clinical trial for the prevention of Clostridium difficile-associated diarrhoea (or disease; CDD), 124 hospitalized patients with CDD received standard antibiotics (vancomycin hydrochloride or metronidazole) and lyophilized *Saccharomyces boulardii* (1 g corresponding to $3x10^{10}$ CFU/ day) or placebo for 4 weeks and were followed up for an additional 4 weeks after therapy. The combination treatment was more effective and safe than standard therapy alone which was not influenced by the choice of standard antibiotic or by the dose per day. Patients receiving *S. boulardii* had significantly fewer daily stools than patients receiving a placebo. S. boulardii did not significantly reduce the colonization frequency of *C. Difficile* but did significantly reduce the frequency of toxin B positivity compared with placebo by the end of week 4. Moreover, multivariate analysis revealed that patients treated with S. boulardii had a significantly lower relative risk (RR) of CDD recurrence compared with placebo. There were no serious adverse reactions associated with *S. boulardii.*

In an open, uncontrolled clinical trial, a group of 25 patients with a mild to moderate clinical flare-up of ulcerative colitis (Truelove and Witts' criteria) received additional treatment with *S. boulardii (*750 mg daily for 4 weeks) during maintenance treatment with high-dose mesalazine (3 g daily). Of the 24 patients who completed the 4-week course with *S. boulardii*, were reported no side effects induced by the probiotic agent. A significant reduction in the clinical index score observed at the end of the treatment. However, the most meaningful clinical result was that a successful outcome (a score of 5 or less) achieved in 17 patients (68 % of cases on an intention-to-treat basis) in all instances, sigmoidoscopy confirmed the clinical remission.

Crohn's disease patients have an altered intestinal flora and a high tendency to experience diarrhoea which often recurs. A total of 32 patients with Crohn's disease in clinical remission (Crohn's Disease Activity Index [CDAI] <150) was randomly treated for six months with either mesalamine (3 g/day) or mesalamine (2 g/day) plus S.

boulardii (1 g daily) to assess efficacy against diarrhoea. Clinical relapses as assessed by CDAI values were significantly higher in patients receiving mesalamine alone than patients in the group treated with mesalamine plus *S. boulardii*. The results suggest that *S. boulardii* may represent a useful tool in the maintenance treatment of Crohn's disease. The clinical benefits of *S. boulardii* administration were not represented by a mere reduction in diarrhoea (a rather predictable effect with a probiotic), but also by an improvement in other clinical parameters (e.g. abdominal pain, general well-being, hematocrit level).

Paediatric patient group:
The published scientific findings on the symptomatic treatment of acute diarrhoea include numerous controlled studies which were carried out in different countries: 4 studies with children aged between 2 weeks and just below 3 years of age (148 children were treated with verum), 1 study with children of 6 months to just below 4 years of age (95 children were treated with verum) and 5 further studies with children from 2 months up to 16 years of age (244 children were treated with verum). In summary, a positive effect on the duration of diarrhoea and the stool frequency could be shown in favour of the verum.

The administered dosage was between 250 mg and 500 mg *Saccharomyces boulardii* per day. The most frequent dosage used as 2 x 250 mg. The duration of administration was between 4 and 7 days. Tolerability was good.

In a multicenter randomized controlled clinical trial for evaluating the efficacy and safety of *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea (AAD) in infants and young children. Hospitalized young children aged between 1 month and 3 years (nongastrointestinal infection and antibiotic therapy required) were involved in the study. The control group received antibiotic therapy for different reasons and other conventional treatment. The prevention group was given additional Saccharomyces boulardii (250 mg/d) orally. During the administration of antibiotics, the incidence of AAD in prevention group was significantly lower than that of control group. Within 14 days after the discontinuation of antibiotics, the percent of new diarrhea cases in prevention group was also significantly lower than that in control group. No adverse effects related with Saccharomyces boulardii were observed in the study. In conclusion, Saccharomyces boulardii is effective and safe to prevent AAD of infants and young

children both during the usage of antibiotics and up to 14 days after drug discontinuance.

5.2 Pharmacokinetic properties (Ref no. 1, page 158&160, no. 3.1; Ref no. 5, page 2207-2208, no. 3.2; Ref no. 7, page 1617, no. 3.3)

Saccharomyces boulardii is taken orally and eliminated via the stools. Published pharmacokinetic studies show that *Saccharomyces boulardii* has a half-life of 6 hours and that less than 5% (independent on the dose) of viable cells can be recovered in the stools.

Viable *Saccharomyces boulardii* cells achieve a stable level within 3 days and are no longer detectable in the stools than 2 to 5 days after completion of the treatment. A permanent colonization does not take place in human beings.

5.3 Preclinical safety data (Ref no. 18)

The preclinical data are incomplete. Due to the long-term medical application, however, there is a sufficient proven safety margin available in human beings.

The results of a mutagenicity study (AMES Test) show that the *Saccharomyces boulardii* does not possess any mutagenic effects in this test system.

Investigations on reproduction toxicity and carcinogenicity are not available.

6. Pharmaceutical Particulars

6.1 List of excipients

Lactose, Magnesium stearate (plant-based), Hypromellose, Purified water, Titanium dioxide

6.2 Incompatibilities

If microbiologically stool examinations are carried out during or shortly after treatment with *Saccharomyces boulardii*, the examining laboratory should be informed about the treatment because otherwise false-positive findings may result.

6.3 Shelf life

Three years from manufacturing date.

6.4 Special precautions for storage (stability data, attached p. 469-499)

Store below 25°C in a dry place and away from direct sunlight.

6.5 Nature and contents of container

Hard capsules in unit carton containing 1x10 and 3x10 capsules blister packed.

6.6 Special precautions for disposal and other handling

Read the instructions carefully before use.

Do not use the product after the expiry date.

Do not use the product if there are any significant changes in appearance of the capsules.

Keep out of reach of children.

7. Marketing Authorization Holder

MEGA LIFESCIENCES Public Company Limited

Samutprakarn 10280, Thailand

8. Marketing Authorization Number

[.....]

9. Date of First Authorization/Renewal of the Authorization:

DD/MM/YYYY

10. Date of Revision of the Text:

MM/YY