1. IDENTIFICATION OF MEDICINAL PRODUCT

Name: BIOFLOR® 250 mg, powder for oral suspension

Qualitative and quantitative composition
Saccharomyces boulardii CNCM I-745....250 mg (lyophilized yeast cells)
Each sachet is required to present a minimum *Saccharomyces boulardii* CNCM I-745 of 2.5 x 10^9 CFU
Excipients: lactose (monohydrate, as freeze-drying carrier of *S. boulardii*), fructose, colloidal anhydrous silica, tutti-frutti flavour (containing sorbitol).

Product description
Paper/aluminium/polyethylene composite sachet containing a very light-brown powder with an odor of fruit.
Appearance after reconstitution: liquid suspension with a milky appearance.

Pharmaceutical form
Sachet: box of 10 sachets.

Pharmacotherapeutic classification
Pharmacotherapeutic group: Antidiarrheal microorganisms. ATC Code: A07FA02

2. PHARMACODYNAMICS
Saccharomyces boulardii (Sb) CNCM I-745 is an antidiarrhoeal yeast probiotic that supports the intestinal microbiota. Pharmacodynamics of *Saccharomyces boulardii* CNCM I-745, live probiotic yeast, have been established on various models by in vitro and in vivo, animal, and human studies which demonstrated it acts at 3 levels:
Luminal action: Sb may interfere with pathogen toxins, preserve cellular physiology, interfere with pathogens attachment (anti-toxinic effect against *C. difficile*, cholera, *E. coli* through preservation of tight junctions, adhesion of the bacteria to Sb enabling to stop the bacterial invasion), interact with normal microbiota or assist in re-establishing short chain fatty acid levels.
Trophic action: Sb, restores fluid transport pathways, stimulates protein and energy production or act through a trophic effect by releasing spermine and spermidine or other brush border enzymes that aid in the maturation of enterocytes. Immune response: Sb increases the IgA levels in the intestine.
Mucosal action – anti-inflammatory effect: Sb may interfere with NF-κB mediated signal transduction pathways which stimulate pro-inflammatory cytokine production.
In lyophilized form, *S. boulardii* CNCM I-745 survives gastric acid and bile and can be detected alive throughout the entire digestive system (if ingested daily in freeze-dried form). *S. boulardii* CNCM I-745 is also resistant to proteolysis. So it acts all along the intestine.

3. PHARMACOKINETICS
Saccharomyces boulardii CNCM I-745 is not absorbed. After repeated oral doses, it transits in the digestive tract without colonizing it, rapidly attaining significant intestinal concentrations which are maintained at a constant level throughout the administration period. *Saccharomyces boulardii* CNCM I-745 is no longer present in the stools 2 to 5 days after discontinuation of treatment.
After 3 days of administration, a stable concentration in the intestinal content is reached. Within 1 week after stopping the administration, *S. boulardii* CNCM I-745 becomes undetectable.
Saccharomyces boulardii CNCM I-745 is not absorbed from the intestinal tract. The number of living yeast cells in faeces decreases fast after discontinued treatment, and 5 days after discontinuation the level hereof is below measurable level.

4. INDICATIONS
• Treatment of acute infectious diarrhoea of infants, children and adults;
• Prevention of antibiotic-associated diarrhoea in children and adults;

• Addition to vancomycin/metronidazole-treatment to prevent recurrence of *Clostridium difficile* diseases in adults;
• Prevention of tube-feeding associated diarrhoea in adults.

5. RECOMMENDED DOSAGE
Infants and children: 1 or 2 sachets daily.
Adults: 1 or 2 sachets, once or twice daily.

Treatment duration:
Treatment of acute infectious diarrhoea of infants, children and adults: approximately **1 week.**
Prevention of antibiotic-associated diarrhoea in children and adults: treatment should be started within **48 to 72 hours** of the beginning of treatment with antibiotics and it should **continue for at least three days and not longer than 4 weeks** after the treatment with antibiotics is ended.
Addition to vancomycin/metronidazole-treatment to prevent recurrence of Clostridium difficile diseases in adults: treatment should be started as soon possible after the beginning of antibiotic treatment and it should continue for **4 weeks.**
Prevention of tube-feeding associated diarrhoea in adults: during the period of tube-feeding.
The maximum duration of treatment in the usual indications is 4 weeks.

6. METHOD AND ROUTE OF ADMINISTRATION
Pour the contents of the sachet in a little amount of water or sweetened beverage, mix, and drink. The powder can also be mixed with food or poured into a baby's feeding bottle. It should not be poured or mixed with very cold or very hot liquids or food nor alcoholic drinks.
BIOFLOR® 250 mg contains living cells. This drug should therefore not be mixed with very hot (over 50°C), iced or alcoholic drinks or food.

7. CONTRA-INDICATIONS
• Hypersensitivity to one of the components;
• Yeast allergy, in particular allergy to *Saccharomyces boulardii*.
• Patients with central venous catheter (see Section Special warnings).
• Critically ill patients or immunocompromised patients due to a risk of fungaemia (See Section Warning and Precautions)
IF IN DOUBT, IT IS ESSENTIAL TO SEEK THE ADVICE OF YOUR DOCTOR OR YOUR PHARMACIST.

8. WARNING AND PRECAUTIONS
Special warnings
Diarrhoea may be the symptom of another, more serious disease. If in adults or children older than 6 years diarrhoea lasts longer than 2 days or if blood occurs in the stool, or the patient develops fever, previous treatment should be reviewed and oral or parenteral rehydration considered. In children below 2 years of age medical consultation is required. After diarrhoea stops, the treatment may be continued for a few days. Administration of the medication does not replace rehydration; when this is necessary. The amount of administered fluids and the route of administration (oral or intravenous) should be adapted to the severity of diarrhoea, age and general health status.

Children below 2 years of age: medical consultation may be required as diarrhoea may be an unspecific symptom of an underlying disease. Appropriate rehydration may be the main method of diarrhoea management in children, with the volume to be assessed on a regular basis.

Children aged 2 to 6 years: appropriate rehydration may be the main method of diarrhoea management in children. The volume of rehydration fluids is to be assessed on a regular basis. Preventive or therapeutic rehydration should be supplemented with oral fluids. It is recommended to prepare ready-to-use rehydration fluids strictly in line with instructions for preparation.
Sodium (Na^+) level should be around 30-60 mmol/litre, lower levels are intended for less severe dehydration cases. Supplementation of chloride (Cl^-) and potassium (K^+) ions may be necessary to

compensate for their loss by the digestive tract. The recommended glucose levels in the used rehydration fluids should be around 74-110 mmol/litre. The addition of hydrolysed proteins or amino acids did not result in a significant improvement of patient hydration or nourishment level.
Children should be frequently administered fluids, i.e. every 15 minutes. The volume of rehydration fluids administered to the patient should correspond with the body mass loss, i.e.:
50-100 ml of water loss causing 5 to 10% body mass loss. For severe or prolonged diarrhoea with concurrent vomiting and refusal to eat, oral or parenteral rehydration should be considered.

Adults and children above the age of 6: if diarrhoea lasts more than 2 days, review the previous treatment and consider oral or parenteral rehydration.

Warnings – Yeast nature related
There have been very rare cases of fungaemia reported mostly in patients with central venous catheter, critically ill or immunocompromised patients, most often resulting in pyrexia. In most cases, the outcome has been satisfactory after cessation of treatment by *Saccharomyces boulardii*, administration of antifungal treatment and removal of the catheter when necessary. However, the outcome was fatal in some critically ill patients (see Section Contra-indications & Section Adverse Effects / Undesirable Effects).

As with all medicines made from living micro-organisms, special attention must be paid to the handling of the product in the presence of patients mainly with central venous catheter but also with peripheral catheter, even not treated with *Saccharomyces boulardii*, in order to avoid any contamination transmitted by the hands and/or the spread of microorganisms by air. Bioflor® should not be opened in patient rooms. Healthcare providers should wear gloves during handling of probiotics for administration, then promptly discard the gloves and properly wash their hands.

Warnings – Ingredients related
BIOFLOR® 250mg powder for oral suspension in sachet contains fructose.
This medicine contains 471.90 mg fructose in each sachet.
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Fructose may damage teeth in case of long term use.
BIOFLOR® 250mg powder for oral suspension in sachet contains lactose.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
BIOFLOR® 250mg powder for oral suspension in sachet contains sorbitol.
This medicine contains 0.10 mg sorbitol in each sachet.

Precautions for use
Patients should be told the need of:
- rehydration (good body hydration) by drinking large amounts of sweet or salted beverages to compensate for fluid loss caused by diarrhoea (daily average water demand of an adult is 2 litres)
- adhering to an appropriate dietary regime by excluding some foods such as: fruit, green vegetables, spicy dishes, frozen products, cold drinks, while favouring grilled meat and rice. The reduction of milk and dairy products intake should also be considered.

9. INTERACTION WITH OTHER MEDICINES
Do not use this medicine at the same time with an antifungal agent (medicine active against fungus infections).
IN ORDER TO AVOID POSSIBLE INTERACTIONS BETWEEN SEVERAL MEDICINES, IT IS ESSENTIAL TO ROUTINELY INFORM YOUR DOCTOR OR PHARMACIST OF ANY OTHER TREATMENT THAT YOU MAY BE TAKING.

10. PREGNANCY AND LACTATION

Pregnancy

There are no reliable animal teratogenesis data. Clinically, no malformative nor foetotoxic effect has been reported to date. However, monitoring of pregnancies exposed to this medicine is insufficient to rule out any risk. As a precautionary measure, it is preferable to weight benefit/risk before using this medicine during pregnancy. Bioflor® 250mg is not recommended for pregnant women.

Breastfeeding

Saccharomyces boulardii is not absorbed into breast milk. As there are no sufficient data available, it is recommended to consider risk-benefit ratio before using Bioflor® 250mg when breastfeeding.

Fertility

No data are available on the effect on fertility.

11. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Saccharomyces boulardii is not absorbed ; there is no risk of driving impairment or inability to use machines.

12. ADVERSE EFFECTS/ UNDESIRABLE EFFECTS

The incidence of undesirable effects has been defined as follows: very common (≥1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥1/10,000, < 1/1,000), very rare (< 1/10,000, including isolated cases), frequency not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

System Organ Class (MedDRA terminology)	**Rare**	**Very rare**	**Unknown**
Skin and subcutaneous tissue disorders		Allergic reactions: pruritus, wheal formation (urticaria), skin rash (local or generalized exanthema), swelling of the connective tissue of the face (angioedema)	
Immune system disorders		Anaphylactic reaction or even shock.	
Gastrointestinal disorders	Flatulence		Constipation
Infections and infestations		Fungaemia in patients with a central venous catheter and in critically ill or immunocompromised patients (see Section Warning and Precautions)	Sepsis (serious blood infection) in critically ill or immunocompromised patients.
General disorders		Thirst	

13. OVERDOSE

Saccharomyces boulardii CNCM I-745 is not absorbed; there is no reason to expect an overdose. In the event of an overdose, no particular action is required.

14. STORAGE
Do not exceed the expiry date shown on the outer packaging.

Special storage precautions
Store away from humidity at a temperature below 30°C.

15. NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER
Product Registration Holder
Servier Malaysia Sdn Bhd - Unit No.25-02, Level 25, Imazium
No.8, Jalan SS21/37, Damansara Uptown
47400 Petaling Jaya, Selangor Darul Ehsan

Name and address of the Manufacturer
BIOCODEX - 1 avenue Blaise Pascal - 60000 BEAUVAIS, France

DATE OF REVIEW OF PACKAGE INFORMATION LEAFLET:
15 May 2025