1. IDENTIFICATION OF MEDICINAL PRODUCT

Name: BIOFLOR® 250 mg, capsules

Qualitative and quantitative composition
Saccharomyces boulardii CNCM I-745....250 mg (lyophilized yeast cells)
Each capsule is required to present a minimum *Saccharomyces boulardii* CNCM I-745 of 2.5 x 10^9 CFU
Excipients of the capsule: lactose, magnesium stearate.
Composition of the capsule shell: gelatin, titanium dioxide (E171).

Product description
Light brown powder in opaque white capsule, with characteristic odor.

Pharmaceutical form
Capsule: Bottle of 10 and 50 capsules - Blister of 30 and 40 capsules.

Pharmacotherapeutic classification
ANTI-DIARRHOEA, Replacement flora (A: digestive system and metabolism).

2. PHARMACODYNAMICS
Saccharomyces boulardii (Sb) CNCM I-745 is an intestinal replacement flora which acts as antidiarrhoeal microorganisms in the digestive tract. 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 reduces mucositis, 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 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
Children (> 6 years old): 1 to 2 capsules daily.
Adults: 1 or 2 capsules, once or twice daily. Capsules should be swallowed with a glass of water.
The capsules can be taken either during, before or after meals. In young children under 6 years of age, it is recommended not to swallow capsules (risk of false passage) and to use the powder for oral suspension in sachet.
Treatment duration:
Treatment of acute infectious diarrhoea of 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
Capsules should be swallowed with a glass of water. In young children under 6 years of age, it is recommended not to swallow capsules (risk of false passage) and to use the powder for oral suspension in sachet.

7. CONTRA-INDICATIONS
• Hypersensitivity to one of the components.
• 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
This drug is a complement of dietetic rules:
• rehydration by abundant, salted or sweetened drinks, in order to compensate for the loss of liquid due to the diarrhoea (the average daily ration of water in adult is 2 liters);
• to feed during the diarrhoea;
• by excluding certain supply and particularly fruits, green vegetables, spiced dishes, as well as food or frozen drinks;
• by privileging roasted meats and rice.
IN CASE OF DOUBT, DO NOT HESITATE TO SEEK THE ADVICE OF YOUR DOCTOR OR YOUR PHARMACIST.
You must consult immediately your physician in the following cases:
• in absence of improvement after 2 days of treatment
• in case of fever, vomiting
• in case of presence of blood or mucus in the stools
• in case of intense thirst, dryness of tongue: these signs show the beginning of the dehydration, that means an important loss of liquid due to the diarrhoea. Your physician will decide the necessity to prescribe a rehydration which could be administered by oral or IV route.
BIOFLOR® 250 mg Capsule contains living cells. This drug should therefore not be mixed with very hot (over 50°C), iced or alcoholic drinks or food.
BIOFLOR® 250 mg Capsule contains lactose.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Because of the risk of generalized *Saccharomyces boulardii* infection, in case of patients with modified immune system (e.g. HIV infection, chemotherapy, irradiation) the drug should be administered only under strict medical control.
It is advisable not to open capsules in the surroundings of patients with a central venous catheter, to avoid any colonization, especially hand-borne, of the catheter. It is advisable not to open the capsules in the surroundings of critically ill or immunocompromised patients due to a risk of airborne contamination.
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).

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

It is not recommended to prescribe this drug during pregnancy and lactation due to lack of sufficient data.
If you discover that you are pregnant during the treatment, consult your physician as only he can decide if it is necessary to go on the treatment.
As a general rule during pregnancy or lactation it is advisable to ask your physician or your pharmacist for advice before taking any medicine.

11. ADVERSE EFFECTS/ UNDESIRABLE EFFECTS

Adverse reactions encountered most often are 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 classes

System Organ Class (MedDRA terminology)	**Rare**	**Very rare**	**Unknown**
Gastrointestinal disorders	Flatulence		Constipation
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.	
General disorders		Thirst	

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.

Very rare cases of fungemia with fewer cases of positive Saccharomyces blood culture have been reported in hospitalized patients with central venous catheter, in immunodepressed patients and in patients with a severe gastrointestinal disease.

12. OVERDOSE
No case reported. If you have taken more Bioflor than you should, contact your pharmacist or your physician for advice.

13. 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.

14. 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:
09 April 2021