For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

This package insert is continually updated: Please read carefully before using a new pack

Spores of polyantibiotic-resistant *Bacillus clausii*
ENTEROGERMINA®
2 billion/capsule

COMPOSITION
One hard gelatin capsule contains spores of polyantibiotic-resistant *Bacillus clausii* - 2 billion (strains: O/C, N/R, SIN and T)
Approved colour used in capsule shell: Titanium dioxide I.P.

PHARMACEUTICAL FORM
Capsules

CLINICAL PARTICULARS
Therapeutic indications
For the treatment of alterations in the intestinal bacterial flora.

Posology and method of administration
Adults*:* 2-3 capsules per day
Children: 1-2 capsules per day
Swallow accompanied by a sip of water or other drinks
Enterogermina® is also available in mini bottles containing oral suspension. For young children who have difficulty in swallowing the hard capsules, it is better to use the oral suspension.

Enterogermina® capsules and mini bottles containing oral suspension are for oral use only. Do not inject or administer in any other way (see Section Special warnings and special precautions for use). Do not use for more than 30 days.

Contraindications
Hypersensitivity to the active substance or to any of the excipients

Special warnings and special precautions for use
Special warnings
This medicine is for oral use only. Do not inject or administer in any other way. Severe anaphylactic reactions, such as anaphylactic shock, have occurred with incorrect route of administration.

There have been reports of bacteremia, septicemia or sepsis in patients taking *Bacillus clausii* who are immunocompromised or are hospitalized due to a serious illness. Enterogermina® should be used in these patients only if the potential benefits outweigh the potential risks.

During treatment with antibiotics, it is recommended that the preparation be administered between antibiotic doses.
Contact your doctor if the condition worsen after 2-3 days of usage.
Keep out of the reach of children.

Interactions with other medicinal products and other forms of interaction.
No interaction studies have been performed

Reproduction
Pregnancy
Limited data are available on the use of probiotics including Enterogermina® in pregnant women. However, no conclusions can be drawn regarding whether or not Enterogermina® is safe for use during pregnancy. Enterogermina® should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

Lactation
There are limited available data on the presence of Enterogermina® in human milk, milk production, or the effects on the breastfed infant. However, no conclusions can be drawn regarding whether or not Enterogermina® is safe for use during breastfeeding. Enterogermina® should be used during breastfeeding only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child.

Driving a vehicle or performing other hazardous tasks
Enterogermina® has no influence on the ability to drive and use machines

Undesirable effects
The following CIOMS frequency rating is used, when applicable:
Very common ≥10%; Common ≥ 1 and <10%; Uncommon ≥0.1 and <1%;
Rare ≥ 0.01 and < 0.1%; Very rare< 0.01%; Not known (cannot be estimated from available data).

Skin and subcutaneous tissue disorders:
During post marketing experience, hypersensitivity reactions, including rash urticaria and angioedema have been reported.

Infections and infestations:
Not known: Bacteremia, septicemia or sepsis in immunocompromised patients or those hospitalized due to a serious illness.

Overdose
No cases of overdose have been reported

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic category: antidiarrhoeal microorganisms
Enterogermina® is a preparation consisting of a suspension of 4 spore strains (SIN, O/C, T, N/R) of *Bacillus clausii*, which naturally occur in the intestine and is non-pathogenic.
When administered orally, *Bacillus clausii* spores cross the barrier of the acidic gastric juice due to their high resistance to both chemical and physical agents, and reach the intestinal tract unharmed, where they are transformed into metabolically active vegetative cells.
Spores can survive heat and gastric acidity, by nature. In an in vitro validated model, *Bacillus clausii* spores were shown to survive in a simulated gastric environment (pH 1.4-1.5) up to 120 minutes (survival rate of 96%). In a model that simulates the intestinal environment (bile and pancreatin saline - pH 8), *Bacillus clausii* spores showed their ability to multiply further

compared to the initial amount, in a statistically significant way (from 109 to 1012 CFU – Colony-Forming Units), starting from 240 minutes after incubation.
In a study conducted in 20 subjects, it was found that in humans, *Bacillus Clausii* spores persist in the intestine and can be found in faeces until 12 days after a single oral administration.
The administration of Enterogermina® helps to restore the intestinal microbial flora altered by dysmicrobism, also known as dysbiosis, resulting from antibiotic therapy and which may be associated with gastrointestinal symptoms, e.g. diarrhoea, abdominal pain and increased air in the intestine.
In two open-label, randomized, and controlled clinical studies, Enterogermina® was shown to reduce the duration of acute diarrhoea in children older than 6 months.
Taken during antibiotic treatment and 7 to 10 days thereafter, Enterogermina® was shown to reduce the incidence of abdominal pain and diarrhoea associated with antibiotic treatment.
The following 2 main mechanisms contribute to the effect of *Bacillus clausii* in restoring the intestinal bacterial flora.

Growth Inhibition of Pathogenic Bacteria
The three *B. clausii* supposed mechanisms of action are: colonization of free ecological niches, which are made no longer available by the growth of other microorganisms; competition in adhesion to epithelial cells, which is particularly relevant for spores in the early and intermediate stages of germination; production of antibiotics and/or enzymes that are secreted within the intestinal environment. In an in vitro study, *Bacillus clausii* spores were shown to have antagonistic activity against Gram-positive bacteria - Staphylococcus aureus, Clostridium difficile, Enterococcus faecium - by producing bacteriocins and antibiotics such as clausin.

Immunomodulatory activity
Orally administered *Bacillus clausii* spores were shown to stimulate the production of Interferon-gamma and increase the CD4+ T Lymphocyte proliferation, in in vitro and in vivo murine models. *Bacillus clausii* also showed the ability to produce several B vitamins, helping to correct vitamin deficiencies in the body resulting from an imbalance in the intestinal bacterial flora.
Furthermore, the high level of artificially induced heterologous resistance to antibiotics makes it possible to create the therapeutic conditions to prevent alteration of the intestinal microbial flora following the selective action of antibiotics, especially those with a broad spectrum of action, or to restore it. Given this antibiotic resistance, Enterogermina® may be administered in between two subsequent administrations of antibiotics.
Antibiotic resistance refers to: penicillins, if not in combination with beta-lactamase inhibitors, cephalosporins (mostly with partial resistance), tetracyclines, macrolides, aminoglycosides (except for gentamicin and amikacin), chloramphenicol, thiamphenicol, lincomycin, clindamycin, isoniazid, cycloserine, novobiocin, rifampicin, nalidixic acid and pipemidic acid (intermediate resistance), metronidazole.

PHARMACEUTICAL PARTICULARS

List of excipients

Microcrystalline cellulose, Magnesium stearate, Gelatine, Titanium dioxide (E171), Purified water.

Incompatibilities
None

Storage
Store at a temperature not exceeding 25°C.

Manufactured by:
Sanofi Healthcare India Private Limited
At: Khasra No. 141 to 143 & 145, Mohabewala Industrial Area, Dehradun -248110 (Uttarakhand).

Bulk capsules manufactured by Opella Healthcare Italy s.r.l., Viale Europa,11 - 21040 Origgio (VA) – Italy

Importer: Sanofi Healthcare India Pvt. Ltd., Bldg No. D6, Gala No. 9, Shree Arihant complex, Retibunder Road, Kalher Bhiwandi, Thane - 421302.

Source:
1. *Bacillus clausii* CCSI v3 LRC dated 12th March 2020
2. Italian SmPC dated February 2021

Updated: June 2023