PACKAGE LEAFLET: INFORMATION FOR THE USER

enterogermina®

2 billion / 5 ml oral suspension

sanofi

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A vial contains:
Active substance:
2 billion spores of poly-antibiotic resistant *Bacillus clausii* {strains SIN, O/C, T, N/R}

3. DOSAGE FORM

Oral suspension.

4. CLINICAL INFORMATION

4.1 Therapeutic indication

- Treatment and prophylaxis against intestinal dismicrobism and subsequent endogenous dysvitaminosis.
- Supportive therapy for recovery of the intestine microbial flora, altered during antibiotic or chemotherapy treatments.
- Acute and chronic gastrointestinal disorders of the infants, due to poisoning or to intestinal dismicrobism and dysvitaminosis.

4.2 Posology and method of administration

Adults: 2 - 3 vials a day. Children: 1 - 2 vials a day. Babies: 1 - 2 vials a day.
Vials: administration at regular intervals. Take the content of the vial as it is or dissolving it in water or other beverages {for example, milk, tea, orange juice}.
This drug product is for oral use only. Do not inject or administer in any other way {refer to item 4.4}.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed on item 6.1.

4.4 Special warnings and precautions of use

Special warnings
Bacteremia/sepsis
Cases of bacteremia, septicemia and sepsis have been reported after the start of marketing in immunocompromised or seriously ill patients and in preterm newborns. In case of some ill patients in critical conditions, the outcome has been fatal. ENTEROGERMINA must be avoided in these groups of patients {refer to item 4.8}.
This drug product is for oral use only. Do not inject or administer through other routes. An incorrect use of the drug product has triggered serious anaphylactic reactions, such as anaphylactic shock.
Use precautions
During an antibiotic treatment, it is advised to administer the preparation in the period in-between administrations of the antibiotic.
The eventual presence of small visible bodies in the vials of ENTEROGERMINA is due to aggregates of spores of *Bacillus clausii* and, therefore, it does not indicate an altered product.
Agitate the vial before using it.

4.5 Interactions with other drug products and other forms of interaction

No study of interaction has been performed.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
No data related to the use of Enterogermina in pregnant women is available; therefore, it is not possible to draw conclusions on regards to the safety of use of Enterogermina during pregnancy.
Enterogermina must be used during the pregnancy only if the potential benefits for the mother overcome the potential risks, including those for the fetus.
Breastfeeding
No data related to the use of Enterogermina during the breastfeeding is available regarding the composition of the breast milk and the effects on the child. It is not possible to draw conclusions on the safety of the use of Enterogermina during the breastfeeding.
Enterogermina must be used during the breastfeeding only if the potential benefits for the mother overcome the potential risks, including those for the breast-fed child.
Fertility
Data regarding the effect of Enterogermina on the human fertility is not available.

4.7 Effects on the ability to drive vehicles and on the use of machinery

Enterogermina does not alter the ability to drive vehicles and use machinery.

4.8 Side effects

During the treatment with this drug product, the following adverse events have been observed, classified according to the MedDRA classification per organ class and based on the following frequency classes:
Very common {2 1/10}; Common {2 1/100, < 1/10}; Uncommon {2 1/1,000, < 1/100}; Rare {2 1/10,000, < 1/1,000}; Very rare {< 1/10,000}; Unknown {frequency could not be defined based on the data available}.

Classification per organ system	Common	Uncommon	Rare	Very rare	Unknown
Infections and infestations					Bacteremia, septicemia and sepsis {in immunocompromised orseriously ill patients} {refer to item 4.4}
Skin and subcutaneous tissue disorders					Hypersensitivity reactions, including rash, hives and angioedema

Opella Healthcare Italy
PACKAGING TEAM

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Reporting of the suspected adverse reactions
The reporting of the suspected adverse reactions occurring after the drug product authorization is important, since it provides an ongoing monitoring of the risk-benefit ratio for the drug product. The health care professionals are required to report any suspected adverse reaction.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTY

5.1 Pharmacodynamics property

Pharmacotherapeutic category: anti-diarrheal microorganisms - ATC Code: A07FA

ENTEROGERMINA is a preparation comprised of a suspension of 4 strains {SIN, O/C, T, N/R} of spores of *Bacillus clausii*, regular hosts of the intestine, devoid of pathogenic power.
Administered orally, the spores of *Bacillus clausii* surpass the barrier of the acid gastric juice thanks to their increased resistance against both chemical and physical agents, reaching unscathed the intestinal tract where their transform into metabolically active vegetative cells.
The spores by their nature are able to survive the gastric warmth and acidity. In a validated in vitro model, the spores of *Bacillus clausii* have shown to survive in a simulated gastric environment {pH 1.4-1.5} up to 120 minutes {survival rate corresponds to 96%}. In a model that simulates the intestinal environment {pancreatin-bile salt solution - pH 8}, the spores of *Bacillus clausii* have shown to be able to multiply further in relation to the initial quantity, in a statistically significant manner {from 109 to 1012 CFU - colony-forming unit}, as of 240 minutes after the incubation.
In a study performed with 20 subjects, it has been found that in men the spores of *Bacillus clausii* remain in the intestine and may be found in the feces up to 12 days after a single oral administration. The administration of ENTEROGERMINA contributes to the recovery of the intestine microbial flora altered during dismicrobisms, also called dysbiosis, resulting from the intake of antibiotic therapy and which may be related to the gastrointestinal symptoms, such as diarrhea, abdominal pain and increase of air in the intestine.
In two randomized, open-label, controlled clinical trials, ENTEROGERMINA has demonstrated to reduce the duration of acute diarrhea in children above 6 months old. When used during the antibiotic treatment and in the 7-10 subsequent days, ENTEROGERMINA has shown to reduce the incidence of abdominal pain and diarrhea related to the antibiotic treatment.
The 2 primary mechanisms, reported below, contribute to the effect of *Bacillus clausii* in the recovery of the intestine bacterial flora.

Inhibition of the growth of pathogenic bacteria

The 3 hypothesized mechanisms of action for B. clausii are: colonization of the free ecological niches, which are made unavailable for the growth of other microorganisms; competition in the adherence to epithelial cells, which is particularly relevant to the spores in the initial and intermediate phases of germination; production of antibiotics and/or enzymes secreted inside the intestinal environment. In an in vitro study the spores of *Bacillus clausii* have shown to produce bacteriocines and antibiotics such as clausine, with an antagonist activity against gram-positive *Staphylococcus aureus*, *Clostridium difficile* and *Enterococcus faecium* bacteria.

Immunomodulatory activity

The spores of Bacillus clausii, administered orally, have shown at in vitro and in vivo murine models to stimulate the production of interferon gamma and to increase the proliferation of TCD4+ lymphocytes. In addition, *Bacillus clausii* has shown the ability to produce various vitamins of the B group, contributing to the correction of the deficiency of vitamin in the body resulting from the imbalance of the intestinal bacterial flora.
Also, the high level of artificially induced heterologous resistance to other antibiotics create therapeutic conditions to prevent the alteration of the intestine microbial flora, by the selective action of antibiotics, particularly those of broad-spectrum action, or to restore it.
Due to such antibiotic resistance, ENTEROGERMINA may be administered in-between administrations of antibiotics.
Antibiotic resistance refers to: penicillins, if not combined with beta-lactamases inhibitors, cephalosporins {partial resistance in most cases}, tetracycline, macrolides, aminoglycosides {except for gentamicin and amikacin}, chloramphenicol, thiamphenicol, lincomycin, clindamycin, isoniazid, cycloserine, novobiocin, rifampicin, nalidixic acid and pipemidic acid {intermediate resistance}, and metronidazole.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Vials: Purified water.

6.2 Incompatibility

None.

6.3 Shelf-life

Vials
2 years
After opening the vial: the preparation should be taken right away, in order to avoid the contamination of the suspension.

6.4 Special precautions for conservation

Store below 30 QC.

6.5 Nature and content of the package

Vials: lithographed cardboard box containing 10 vials.

6.6 Special precautions for the disposal and handling

Vials: agitate the vial before using.

7. Manufacturer

Opella Healthcare Italy S.r.l. - Viale Europa, 11 21040 Origgio {Va} Italy

REFERENCES

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LOCAL REVIEW

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927663 - IST ENTEROGERMINA 2MLD BT10 S4 XE

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