Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to relevant sections of the Product Information

The existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below]

Summary of product characteristics

4.1 Therapeutic indications

The wording of the indication should be deleted and the text below should be inserted in its place:

Irritable bowel syndrome

4.2 Posology and method of administration

The text below should be inserted by replacing the existing text of this section:

Posology

Adults:

At the beginning of the treatment: 10 drops three-times daily.

After one week, the dose is increased to 20 drops three-times daily.

If signs of gastrointestinal symptoms like flatulence, diarrhoea, abdominal pain or abdominal discomfort worsen or occur more frequently at the beginning of the treatment, Symbioflor E. coli should be taken diluted in water, or the dose should be reduced or the number of drops should be increased more slowly.

Paediatric population:

The efficacy and safety in children and adolescents have not been established. Available data are described in sections 4.8 and 5.1.

Method of administration

The drops are taken orally during the meals. If necessary, they can be diluted in water (see above).

Duration of treatment

Duration of use of 8 weeks is recommended.

If symptoms worsen during treatment or persist after 8 weeks of treatment, the patient should seek medical advice.

Efficacy and safety beyond 8 weeks have not been studied.

4.3 Contraindications

The text below should be inserted by replacing the existing text of this section:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe organic diseases of the gastrointestinal tract such as acute cholecystitis, acute pancreatitis, ileus, as well as cachexia and marasmus.

4.4 Special warnings and precautions for use

The text below should be inserted by replacing the existing text of this section:

Prior to a diagnosis of ‚irritable bowel syndrome', organic causes of the gastrointestinal disorders must be excluded.

During acute febrile diseases, Symbioflor *E. coli* should be temporarily discontinued.

Symbioflor *E. coli* should not be taken during a treatment with antibiotics or within 5 days after the end of such a treatment (see also section 4.5).

If symptoms are more severe, e.g. acute diarrhoea with high fever or with blood in stool or the diarrhoea lasts longer than 2 days, or if other, longer-lasting or unexplained gastrointestinal symptoms occur, treatment should be discontinued and a doctor should be consulted.

4.8 Undesirable effects

The text below should be inserted by replacing the existing text of this section:

Summary of safety profile

The most common undesirable effects observed in the clinical trial, predominantly observed within the first 4 weeks of treatment, were abdominal pain and urticaria. These reactions usually disappear within a few days even if treatment is continued.

Tabulated list of adverse reactions

The evaluation of undesirable effects is based on the following frequencies:

Very common (≥1/10)

Common (≥1/100 to <1/10) Uncommon (≥1/1,000 to <1/100) Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000)

not known (cannot be estimated from the available data) The following undesirable effects may occur:

Immune system disorders Common: urticaria

Gastrointestinal disorders

Common: abdominal pain (including upper abdominal pain and abdominal discomfort).

Not known: flatulence, nausea, diarrhoea.

Gastrointestinal symptoms

If gastrointestinal symptoms (like abdominal pain, flatulence or diarrhoea) worsen or occur more frequently at the beginning of the treatment, please refer to section 4.2 for measures to be taken to reduce or avoid these symptoms.

Paediatric population

In a non-interventional study with 203 children aged 4-18 years no undesirable effects were reported. Only limited experience of adverse reactions in children from pharmacovigilance data is available. However, based on these limited data the safety profile for children and adolescents is considered to be comparable to that of adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (details see below). *[To be filled in nationally]*

4.9 Overdose

The text below should be inserted by replacing the existing text of this section**:**

In a non-interventional post-marketing high-dose safety study in healthy volunteers, two of five subjects experienced side effects. Only non-serious and already known side effects as described in section 4.8 were reported upon administration of single doses up to 20 times higher than the recommended daily dose.

5.1 Pharmacodynamic properties

The text below should be inserted by replacing the existing text of this section:

Pharmacotherapeutic group: Other immunostimulants, Antidiarrheal microorganisms ATC code: L03AX, A07FA

Mechanism of action

Escherichia coli, the active substance in Symbioflor *E. coli*, is a living bacterium that is present in the healthy intestinal flora of humans.

An in-vitro study carried out using polymerase chain reaction (PCR) to investigate the effects of Symbioflor *E. coli* on epithelial cells (SW 480) from the human intestinal mucosa showed an up-regulation of the cytokines IL-1β, TNF-α, GM-CSF and the chemokine IL-8.

The qualitative effect on the gene expression in the mucosal epithelial cells, the key control elements of immune function in the human intestine, is similar to that exerted by the natural, physiological intestinal flora.

In a human whole-blood culture model, Symbioflor *E. coli* exerts strong modulating effects on the physiologically induced synthesis and release of cytokines and chemokines. Overall, there is a shift in activity in favour of Th1 helper cells, accompanied by inhibition of the Th2 helper cells. If and to what extend these results are applicable for the use in patients is not yet known.

Clinical efficacy and safety

A clinical trial including 298 patients with irritable bowel syndrome recruited in primary care centres showed a good or very good treatment success on Symbioflor E. coli in 62.9 % of the patients and in 39.4 % of the patients treated with placebo based on the investigator's global assessment of efficacy on a 4-point rating scale

Efficacy was confirmed when using two post-hoc defined patient assessed endpoints, i.e. patient's assessment of symptoms and abdominal discomfort/pain comprising each of 8 or respectively 5 IBS relevant symptoms. The number of patients free of all the assessed IBS relevant symptoms after the treatment period of 8 weeks was significantly higher for Symbioflor E. coli treatment compared to placebo

Overall, Symbioflor E. coli was well tolerated in the clinical trial with no significant differences in the tolerability compared to placebo regarding vital functions, body weight and all laboratory parameters tested. Only non-serious adverse events were recorded with a slightly higher frequency for Symbioflor

E. coli. The investigator's global assessment of tolerability was predominantly good to very good and balanced between Symbioflor *E. coli* and placebo.

In a non-interventional study with 203 children aged 4 – 18 years, that were diagnosed for having IBS based on the ROM III criteria for children, the overall assessment of efficacy for all 4 IBS subtypes was very good to good in more than 80 % of the children for both, the physician's and the patient/parent's assessment. In the group of children aged 12 – 18 years with the IBS subtype "pain + alternating diarrhoea and constipation" the physician's and patient/parent's assessment of efficacy was lowest (55 % or 66 %, respectively).

The overall assessment of tolerability was good to very good in more than 98 % of the children for both, the physician's and the patient/parent's assessment (see also section 4.8).

5.2 Pharmacokinetic properties

The text below should be inserted by replacing the existing text of this section:

E. coli bacteria are not absorbed but act locally at the intestinal immune system.

In an in-vitro gastric exposure model mimicking the human stomach and ileus under fasting conditions 1 ml (less than a single dose) of Symbioflor *E. coli* was tested for the survivability of the *E. coli* production strain. In this model enough bacteria of the *E. coli* strain survived the acid stomach passage so that their number increased again when they reached the small intestine conditions. When the same volume was tested in the SHIME model (Simulation of the Human Intestinal Microbial Ecosystem) under conditions simulating food intake fewer bacteria were killed in the stomach while their numbers were relatively stable in the conditions simulating the upper gastrointestinal tract.

The high dose study (see section 4.9) demonstrated that the specific *E. coli* strain cultivates the human gut at least for days but also for up to months after a single dose.

The *E. coli* bacteria are excreted via the faeces.

Package leaflet

Section 2 What you need to know before you take Symbioflor *E. coli*

The text below should be inserted by replacing the existing text of this section**:**

Do not take Symbioflor *E. coli*:
- if you are allergic to *Escherichia coli* bacteria or any of the other ingredients of this medicine (listed in section 6).

- if you have severe organic diseases of the gastrointestinal tract such as acute inflammation of the gallbladder or pancreas, or intestinal obstruction.

- if you have very severe abnormal weight loss or extreme weight loss due to malnutrition (cachexia, marasmus).

Warnings and precautions

Talk to your doctor or pharmacist before taking Symbioflor *E. coli*.

Prior to a diagnosis of 'irritable bowel syndrome', your doctor should exclude organic causes of the gastrointestinal disorders.

Do not take Symbioflor *E. coli* during acute illnesses with fever. Please interrupt treatment, temporarily.

Do not take Symbioflor *E. coli* during a treatment with antibiotics or within 5 days after the end of such a treatment (see also section 4.5).

Consult a doctor and stop treatment if symptoms are more severe, e.g. acute diarrhoea with high fever or blood in stool, or the diarrhoea lasts longer than 2 days, or other, longer-lasting or unexplained gastrointestinal symptoms occur.

Other medicines and Symbioflor *E. coli*

Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

Antibiotics may inhibit the *Escherichia coli* bacteria and thus reduce the efficacy of this medicine.

Symbioflor *E. coli* with food and drink
Take the drops during meals (see section 3 How to take Symbioflor *E. coli*)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Although there are no known harmful effects of Symbioflor *E. coli* on the unborn child, the drops should be used during pregnancy and when breast-feeding only after a careful benefit-risk assessment by the doctor.

Driving and using machines

Symbioflor *E. coli* has no or negligible influence on the ability to drive or use machines.

Section 3 How to take Symbioflor *E. coli*

The text below should be inserted by replacing the existing text of this section:

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

Adults take 10 drops orally three-times daily during meals at the beginning of treatment. After one week, increase the dose to 20 drops three-times daily.

If signs of gastrointestinal symptoms like flatulence, diarrhoea, abdominal pain or abdominal discomfort worsen or occur more frequently at the beginning of treatment, Symbioflor *E. coli* should be taken diluted in water, or the dose should be reduced or the number of drops should be increased more slowly.

Duration of use of 8 weeks is recommended.

If symptoms worsen during treatment or persist after 8 weeks of treatment, seek medical advice.

Use in children and adolescents

No recommendation on a posology can be made as the efficacy and safety in children and adolescents have not been established.

Shake Symbioflor *E. coli* well before use. This will cause slight turbidity.

Symbioflor *E. coli* contains no preservatives and is therefore susceptible to contamination in the event of improper use. This can be prevented by opening the bottle for a short time only when using this product, and by dispensing the drops carefully. Do not touch the dropper. Because of the high surface tension of Symbioflor *E. coli*, problems with starting and stopping release of the drops of solution cannot be completely avoided. Release of the drops is started by holding the bottle at an angle and tapping lightly on the bottom. The speed at which the drops come out can be changed by varying the angle at which the bottle is held.

If you take more Symbioflor *E. coli* than you should

No countermeasures are necessary.

If you forget to take Symbioflor *E. coli*

Do not take a double dose to make up for a forgotten dose, but continue taking the dosage prescribed.

If you stop taking Symbioflor *E. coli*

No special measures are indicated. If appropriate, speak to your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Section 4 Possible side effects

The text below should be inserted by replacing the existing text of this section:

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following undesirable effects may occur:

Common (may affect up to 1 in 10 patients):

- Abdominal pain (including upper abdominal pain and abdominal discomfort)
- Hives

These reactions usually occur within the first 4 weeks of treatment and disappear within a few days even if treatment is continued.

Not known (cannot be estimated from the available data):

- Flatulence
- Nausea
- Diarrhoea

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system: *[to be filled in nationally]*

By reporting side effects, you can help provide more information on the safety of this medicine.