Human Biome

Characteristics of the service of producing donor gut microbiota preparations in the form of a suspension (MBiotix® HBI) and capsules (Mbiotix® HBI Caps)

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Clause: *MBiotix® HBI Caps* and *MBiotix® HBI* suspension kits, produced as a result of the service of producing donor gut microbiota preparations from the donor faeces, in accordance with the guidelines of Scientific Societies and current medical knowledge, are recommended for the treatment of recurrent *Clostridoides difficile* infections where standard therapy has been ineffective and other experimental therapeutic indications. The qualification of the patient for fecal microbiota transplantation (FMT) and the decision on the method of performing the procedure is made by a physician. These services, by assigning unique codes, are additionally subjected to monitoring. This will allow for the rapid identification of new safety information. We provide the service of processing the donor gut microbiota into suspension (*MBiotix® HBI*) and capsules (*MBiotix® HBI Caps*) only on medical prescription. Any adverse reactions should be reported immediately.

1. Type of the service

The service of producing donor gut microbiota preparations in the form of a suspension – *Mbiotix® HBI* – a kit containing two syringes of 100 ml each.

The service of producing donor gut microbiota preparations in the form of capsules – *Mbiotix® HBI Caps* – a set containing 6 jars with capsules that release at the ileocecal area.

2. Qualitative and quantitative composition

MBiotix® HBI – gut microbiota at a concentration of 30 g of starting material (donor faeces) in 100 ml of 0.9% NaCl containing 10^{13} live bacterial cells and glycerol. The preparation has a volume of 100 ml for patients weighing ≤35kg and 200 ml for patients weighing >35kg.

MBiotix® HBI Caps – gut microbiota suspension obtained by centrifugation of a solution containing 60 g of starting material (donor faeces) suspended in 200 ml of 0.9% NaCl and glycerol. A set of capsules contains 10^{13} live bacterial cells, a single capsule contains 10^{12} live bacterial cells.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

There are no legal regulations in Poland enabling for the categorizing the pharmaceutical form based on regulatory documents.
Physicochemically:
- *MBiotix® HBI* – liquid, gut microbiota suspension to be administered via a syringe kit. The kit consists of 100 ml syringes containing a clear liquid – suspension of gut microbiota from a healthy donor with the addition of glycerol.

- *MBiotix® HBI Caps* – enteric-coated capsules containing a centrifuged, thick suspension of gut microbiota. The set consists of jars with capsules in a double coating (acid-resistant and enteric) containing a suspension of gut microbiota from a healthy donor with the addition of glycerol.

4. Clinical particulars

4.1 Therapeutic indications

Recommended treatment regimen for *MBiotix® HBI* and *MBiotix® HBI Caps* – see section 4.3.

Preparations *MBiotix® HBI* and *MBiotix® HBI Caps*, obtained as a result of processing material (faeces) from a healthy donor, are recommended for recurrent and resistant to standard treatment *Clostridioides* (formerly *Clostiridium*) *difficile* infections and for experimental indications with the approval of the Bioethics Committee.

The use of the *MBiotix® HBI* gut microbiota suspension and *MBiotix® HBI Caps* should be in accordance with official recommendations.

4.2 Posology and method of administration

IMPORTANT!

MBiotix® HBI Caps SHOULD BE GIVEN TO THE PATIENT FROZEN, IMMEDIATELY AFTER REMOVING FROM THE FREEZER – DEFROSTED PRODUCT IS NOT SUITABLE FOR ADMINISTRATION OR REFROSTING – read carefully section 4.3.8.a

THE SUSPENSION IN THE SYRINGE KIT *MBiotix® HBI* MUST BE DEFROSTED BEFORE ADMINISTRATION – DEFROSTING SHOULD BEGIN 4-5 HOURS BEFORE THE PLANNED FECAL MICROBIOTA TRANSPLANTATION.

The preparation does not require special defrosting conditions. The syringes should be left in the open packaging until clear, liquid suspension is obtained. DEFROSTED PRODUCT IS NOT SUITABLE FOR REFROSTING – read sections 4.3.8. b – f carefully (depending on the method of administration).

Recommended treatment regimen for *MBiotix® HBI* and *MBiotix® HBI Caps* – see below.

The MBiotix® HBI preparation in a form of suspension, obtained as a result of processing material (faeces) from a healthy donor into a gut microbiota suspension, should be administered via: colonoscope, gastroscope, duodenal/gastric/enteric tubes, PEG, rectal enema. MBiotix® HBI Caps should be administered orally if no contraindications exist – see section 4.3.a.

The method of performing the procedure is always decided by the physician in consultation with the patient.

For best therapeutic results, each patient should be properly prepared before undergoing Fecal Microbiota Transplantation.

4.3 Patient preparation

1. Determine the indications and contraindications for starting therapy.
2. Confirm that the indication for Fecal Microbiota Transplantation is *Clostridioides difficile* infection (CDI) – it is recommended to consider/apply FMT in cases of first and subsequent recurrences of CDI, fulminant CDI, severe CDI unresponsive to 48h of standard therapy, and moderate CDI unresponsive to 7 days of standard therapy. Treatment of *Clostridioides difficile* infections in the above-mentioned, recommended indications with FMT does not require the approval of the Bioethics Committee.
   In cases where FMT is used for indications other than CDI, approval from the Bioethics Committee must be obtained.
3. Rule out alternative diagnoses and perform differential diagnosis.
4. Confirm the absence of absolute contraindications to the administration of the therapy.

5. Confirm obtaining patient consent for treatment with Fecal Microbiota Transplantation.

6. Administer test FMT capsule (applies to the administration of *MBiotix® HBI Caps*)
    - The patient should swallow the test capsule under the care of a physician/nurse to rule out the possibility of chocking.

7. Recommendations for the concomitant treatment
    - According to the recommendations in recurrent C. *difficile* infections, it is recommended to administer vancomycin in doses of at least 4 x 125 mg before the planned FMT, for a period of at least 10-14 days (literature data indicate that **vancomycin treatment for 4 days may already be effective** with subsequent administration of microbiota) or fidaxomicin in doses of 2 x 200 mg for a period of 10 days.

    - The administration of antibiotics to the patient should be stopped for a minimum of 24-48 hours before the administration of *MBiotix® HBI* and/or *MBiotix® HBI Caps*. Taking antibiotics at the same time may reduce the effectiveness of the therapy.

    - The day before FMT, the patient should be given laxatives. It is recommended to cleanse the lower gastrointestinal tract as for colonoscopy, regardless of the chosen transplantation method – it applies also to the capsules. From that moment (start of the cleansing), the patient should be on a strict diet (can take only fluids).

    - 24 hours before administering the preparation via the upper gastrointestinal tract (does not apply to capsules) it is recommended to administer a proton pump inhibitor (IPP) orally in standard doses twice a day. It is recommended to maintain treatment for two days after procedure.

    - One hour before performing FMT with capsules, gastric tube, duodenal/enteric tube or gastroscopy – it is recommended to administer an antiemetic to the patient (8 mg ondansetron orally or intravenously).

    - On the day of FMT administration, in the case of patients with accelerated intestinal transit, it is recommended to administer loperamide – dose just before taking FMT 2mg – 4mg and one hour (and possibly 6h) after taking FMT 1 – 2 mg to slow down gastrointestinal transit. Loperamide is not recommended in patients at high risk of developing toxic toxic megacolon or gastrointestinal paralytic ileus and in the case of administration of gut microbiota preparation in capsules, unless gastrointestinal transit is evidently accelerated.

8. Recommendations for procedures on the day of FMT administration
    - The patient should continue taking IPP if appropriate (as mentioned above).
    - The patient should receive only fluids and oral medications (except for contraindicated ones, such as antibiotics – a relative contraindication).

- In the case of FMT administration under general anaesthesia (colonoscopy, gastroscopy) – the patient should be properly prepared and stop taking fluids.
- In the case of rectal administration of FMT, it is recommended to perform an enema before the procedure to cleanse the colon if colon cleansing with oral preparations has not been performed.

a) FMT administration via capsules – *MBiotix® HBI Caps*

IMPORTANT!

MBiotix® HBI Caps SHOULD BE GIVEN TO THE PATIENT FROZEN, IMMEDIATELY AFTER REMOVING FROM THE FREEZER – DEFROSTED PRODUCT IS NOT SUITABLE FOR ADMINISTRATION OR REFROSTING.

- Enter the preparation code in the documentation and patient consent form to allow monitoring of the therapy.
- Capsules should be administered under the care of a physician/nurse.
- Capsules must be frozen at the time of administration. If the capsules are removed from the freezer but not given to the patient, they must be placed back in the freezer immediately (max. 15 min after removal) or disposed of.
- Before administering capsules with gut microbiota, assess the patient's ability to swallow large capsules, e.g. by giving the patient a test capsule. Each *MBiotix® HBI Caps* kit includes a transparent jar containing two test (empty) capsules.
- Ensure that the patient has an adequate amount of water to swallow the capsules.
- Remove a single jar from the freezer, check the expiration date again, and note the time of removal from the freezer.
- Open the jar by removing the protection.
- Capsules from a single jar should be taken within 15 minutes of removal from the freezer.
- The time to administer the contents of the next jar depends on the patient's readiness. The entre preparation (6 jars) should be taken within one day (unless decided otherwise).
- It is recommended that the patient stay in at least a semi-sitting position for up to 2h after completing the administration of the capsules.
- Two hours after taking the last capsule, the patient can return to an easy-to-digest diet, and then to a normal diet.

Please read the additional information regarding *MBiotix® HBI Caps*

MBiotix® HBI Caps have a solid colour and are odourless. Do not take a damaged capsule. If you notice: a crack, breach in the continuity of both shells, or exposure of the interior of the capsule, discard (do not take) such a capsule.
A loss of 10% of the preparation does not affect the therapeutic effect of fecal microbiota transplantation.

Any damage should be documented with a photograph and reported to the attending physician and the medical representative of Human Biome S.A.
Taking a frozen capsule does not cause frostbite of the gastrointestinal tract.

b) FMT administration via gastric tubes or PEG- *MBiotix® HBI*

- To avoid the risk of vomiting, it is recommended to administer an antiemetic, such as 8 mg ondansetron, 1 to 2 hours before the procedure.
- Before connecting the preparation to the tube, prepare a syringe adapter or a transition connector to the Flocare tube (if applicable and such a tube is used). Tube adapters are included in the bag attached to the package with the syringes.
- To reduce the risk of aspiration/vomiting, place the patient in a 45 – 90 degrees position.
- Before administering the preparation (*MBiotix® HBI*), administer 50 ml of physiological saline into the tube to assess its patency and ensure there are no signs of choking (test).
- After checking and confirming that the end of the tube is placed in the stomach, insert/remove the syringe adapter or connect the transition connector to the Flocare tube (depending on the type of tube used).
- After administering physiological saline, tightly connect the syringe kit to the tube and slowly, i.e. at a rate not exceeding 5 ml – 10 ml / minute, administer *MBiotix® HBI* (two syringe kits, 200 ml of preparation in total; administration time should not be less than 20 minutes).
- After administering *MBiotix® HBI*, administer approximately 50 ml of physiological saline into the tube to rinse the drains.
- To minimize the risk of vomiting/aspiration, the tube should be removed at least 30 minutes after the infusion is completed (optimally, it is recommended to remove the tube one to two hours after the FMT; this does not apply to administration via PEG).
- It is recommended that the patient stay in a sitting position for the first 2h after the FMT is completed.

c) FMT administration via duodenal/enteric tubes – *MBiotix® HBI*

- After inserting the tube with the intention of placing it in the duodenum/jejunum, check its correct placement by an X-ray. The tube can be placed in advance, and after two hours, the position of the tube end should be checked by X-ray; inserting the tube under X-ray fluoroscopy (performing real-time X-ray) or under ultrasound or gastroscopic guidance is recommended, as this accelerates the final placement of the tube end in the appropriate position.
- To avoid the risk of vomiting, it is recommended to administer an antiemetic, such as 8 mg ondansetron, 1 to 2 hours before the procedure.
- Before connecting the preparation to the tube, prepare a syringe adapter or a transition connector to the Flocare tube (if applicable and such a tube is used). Tube adapters are included in the bag attached to the package with the syringes.
- After checking and confirming that the end of the tube is placed in the duodenum/jejunum, insert/remove the syringe adapter or connect the transition connector to the Flocare tube (depending on the type of tube used).
- To reduce the risk of aspiration/vomiting, place the patient in a 45 – 90 degrees position.
- Before administering the preparation (*MBiotix® HBI*), administer 50 ml of physiological saline into the tube to assess its patency and ensure there are no signs of choking (test).

- After administering physiological saline, tightly connect the syringe kit to the tube and slowly, i.e. at a rate not exceeding 5 ml – 10 ml / minute, administer *MBiotix® HBI* (two syringe kits, 200 ml of preparation in total; administration time should not be less than 20 minutes).
- After administering *MBiotix® HBI*, administer approximately 50 ml of physiological saline into the tube to rinse the drains.
- To minimize the risk of vomiting/aspiration, the tube should be removed at least 30 minutes after the infusion is completed (optimally, it is recommended to remove the tube one to two hours after the FMT).
- It is recommended that the patient stay in a sitting position for the first 2h after the FMT is completed.

d) FMT administration via colonoscope – *MBiotix® HBI*

- The syringe tip, with or without a "narrowing," containing Mbiotix® HBI, is adapted to the working channel of the colonoscope and does not require additional adapters.
- It is recommended to administer the entire preparation (200 ml) in the ileocecal region, or if decided, to administer the first portion, approximately 100 ml of the preparation, in the ileocecal region, and subsequent portions of 50 ml each in the hepatic flexure region and then the splenic flexure region of the colon.
- It is recommended that the patient stay in a lying position for two hours after colonoscopy administration of the preparation. If possible, the Trendelenburg position is recommended for the first 15 – 30 minutes, and the preparation should be retained in the gastrointestinal tract for at least 15 – 30 minutes.

e) FMT administration via rectal enema – *MBiotix® HBI*

- The patient should assume the Trendelenburg position on their back.
- The preparation can be administered directly into the rectal cannula, slowly, while monitoring the patient's reactions and tolerability, or it can be placed in a drip infusion bag and administered gravitationally.
- In order to retain the preparation in the rectum/colon for at least 15 – 30 minutes, it is recommended to insert a Foley catheter, inflate and seal the balloon (to block the rectal outlet), and administer the preparation through this catheter.
- If the patient is mobile, it is recommended that they rotate 180 degrees from the left lateral position to the right lateral position and contrariwise every 5 minutes to move the preparation to the right half of the colon and ascending colon.
- It is recommended to retain the preparation in the rectum for about 30 minutes (as mentioned above).

f) FMT administration via gastroscope – *MBiotix® HBI*

- The syringe tip, with or without a "narrowing," containing *Mbiotix® HBI*, is adapted to the working channel of the colonoscope and does not require additional adapters.
- The preparation should be administered carefully (recommended over a minimum of 5 minutes) through the working channel of the gastroscope behind the ligament of Treitz in the small intestine, and if this is not possible – into the duodenum, and then the channel should be rinsed with physiological saline.
- It is recommended that the patient stay in a sitting position for 2h after the FMT is completed.

- It is recommended to consider administering an antiemetic (e.g. 8 mg ondansetron) before the gastroscopy.

9. After FMT administration - *MBiotix® HBI/ MBiotix® HBI Caps*:

- It is recommended that two hours after the FMT, the patient stay in at least a semi-sitting position when administered through the upper gastrointestinal tract, and in a lying/Trendelenburg position when administered via colonoscopy or rectal enema.
- The patient should not drink or eat for two hours after the FMT. This will ensure proper passage of the preparation to the colon and minimize the risk of vomiting.
- Afterward, the patient can return to an easy-to-digest diet. It is recommended to continue an easy-to-digest diet or so-called "healthy diet" (rich in vegetables, fruits, and unprocessed foods) for two weeks following the FMT.
- After the recommended period, the patient can return to a diet decided by the physician/dietitian (normal diet).

4.4 Contraindications

- for administering capsules – oropharyngeal dysphagia, so-called upper (oesophageal) or lower dysphagia, functional dysphagia, neuromuscular dysphagia (e.g. resulting from a stroke, multiple sclerosis, amyotrophic lateral sclerosis) or when the patient shows signs of dysphagia after the capsule is administered in a "safety test;"
- for administering capsules or administration via duodenal/gastric tubes/PEG – a history of aspiration (choking);
- for administering capsules and, relatively, administration via gastric tube – a history of gastroparesis;
- for administering capsules – a history of intestinal obstruction;
- for administering in any form – severe food allergies (anaphylactic or pseudo-anaphylactic reactions in the past) with a history of anaphylactic shock;
- for administering in any form, if another FMT is necessary – if a serious adverse event occurred during a previous FMT administered via the same route, and the connection to the FMT has not been excluded despite following all procedures, it is recommended to choose a different route for the next FMT administration;
- for administering capsules – patients who are allergic to any ingredient of the capsule (hypromellose, gellan gum, titanium dioxide, hypromellose AS);
- in any case where the attending physician thinks that the treatment may pose a threat to the patient's health and/or life;
- antibiotic therapy used at the time of the planned FMT (relative contraindication, reducing the effectiveness of the therapy);
- when the patient cannot be administered FMT through either the upper or lower gastrointestinal tract;
- severe hepatic impairment in the stage of decompensation (the decision is made by the physician, considering the risks and potential benefits).

4.5 Special warnings and precautions for use

Caution: Human Biome S.A. does not exclude the presence of food allergens (nuts, seafood, gluten, lactose) from the Donors diet in the processed donor material. Fecal Microbiota Transplantation (FMT) carries a potential risk of transmitting known and unknown communicable and non-communicable diseases. Literature reports a risk of aspiration with gut bacteria and death (a risk of approximately 0.02%.)

It is recommended to evaluate the effectiveness of the therapy according to the guidelines in the particular condition that was the indication for therapy.

4.6 Interaction with other medicinal products and other forms of interaction

As this is a natural product, no strictly pharmacological interactions with other drugs have been described. However, effective administration of FMT may alter the absorption of drugs.

4.7 Fertility, pregnancy and lactation

As this is a natural product, no negative effects of FMT on fertility, pregnancy and lactation have been described. However, effective administration of FMT may alter the absorption of drugs, including contraceptives.

4.8 Effects on ability to drive and use machines

As this is a natural product, FMT has no negative effects on the ability to drive and use machines.

4.9 Undesirable effects

SAFETY PROFILE

SUMMARY (as of the date of the current version of the document):

- Analysis of fecal microbiota transplantation (FMT) procedures performed over the last two decades revealed that adverse reactions occurred in 19% of all recipients.
- The majority of adverse reactions was mild to moderate in severity and self-limiting in nature.
- Serious adverse reactions occurred in 1.39% of recipients.
- The risk of a serious adverse reaction due to microbiota was estimated at 0.99% (42/4241 cases).
- Serious adverse reactions were reported predominantly in patients who received FMT for C. *difficile* infection and who received transplants through the upper gastrointestinal tract.

- The risk of death due to microbiota was estimated at 0.02% (1/4241 cases).

4.9.1 Data source

In 2020, a systematic review of safety reports on fecal microbiota transplantation (FMT) was conducted, including original publications that appeared between 2000 and 2020 in English and Chinese. The analysed reports (n=129) describe FMT procedures (n=5,688) performed in patients (n=4,241) in randomised clinical trials (n=20), prospective cohort studies (n=29), retrospective studies (n=25) and presented in case series and reports (n=55). The review is currently the richest source of knowledge on the safety of FMT and includes data on the safety of treatment in a representative patient population, including both selected groups participating in controlled clinical trials and the broader population of patients participating in uncontrolled trials and therapeutic experiments.

4.9.2 Types and incidence of adverse reactions

The most common indications for using FMT were recurrent and refractory *Clostridioides* (formerly *Clostridium) difficile* infections (n=2,358), ulcerative colitis (n=743), and Crohn disease (n=295). In addition, the group of patients with various non-specific inflammatory bowel diseases included 350 patients. The review included reports describing FMT administration by different routes, and distinguished between adverse reactions related to microbiota transplantation itself (as a procedure and the active "substance") and the route of administration.

Overall, the review identified 85 types of adverse reactions that occurred 1,347 times during 5,688 FMT procedures. Fifty-four types of adverse reactions were identified as related to FMT. They occurred 1,055 times during 5,688 FMT procedures (Table 1), The most common adverse reactions included diarrhoea, abdominal discomfort, pain, cramping, nausea or vomiting, and bloating.

Adverse reaction	Incidence, n (%) (N=5,688 FMT procedures)
Diarrhoea	569 (10.00%)
Abdominal discomfort,pain, cramping	418 (7.35%)
Nausea, vomiting	188 (3.31%)
Bloating	184 (3.23%)
Constipation	108 (1.9%)
Fever	106 (1.71%)
Fatigue, malaise	75 (1,32%)
Rectal tenesmus	43 (0.76%)
Proctalgia	27 (0.46%)
Breathing difficulties associated with endoscopy	22 (0.39%)
Recurrence of the underlying pathology	21 (0.37%)
Eructation, regurgitation	19 (0.33%)
Exacerbation of symptoms of the underlying pathology	16 (0.28%)
Blood in the stool	12 (0.21%)
Sore throat, rash, redness of the skin, itching	8 (0.14%)

Discomfort associated with not having meals (anorexic), headache	7 (0.12%)
Aspiration pneumonia, CMV infection, rectal bleeding, chills	6 (0.11%)

Table 1. Adverse reactions related to FMT occurring in more than 0.1% of all analysed procedures.

4.9.3 Serious adverse reactions and deaths

Serious adverse reactions were reported in 246 patients, and in 59 cases were assessed by the review authors as related to FMT. The majority of cases (n=42) were associated with the gut microbiota itself, and the remainder (n=17) to the method of transplant administration. The risk of a serious adverse reaction caused by microbiota was estimated at 0.99% (42/4241 cases). All serious adverse reactions occurred in the group of patients who had mucosal damage associated with underlying pathology, such as C. *difficile* infections, inflammatory bowel diseases, cardiovascular diseases and others. The incidence of serious adverse reactions related to FMT was statistically significantly higher in the group of patients with mucosal damage compared to those without such damage ($P<0,05$).

The review identified 108 cases of death following FMT. Of these, 103 were associated with significant comorbidities, while 5 were assessed as related to FMT (4 definitively related and 1 probably related). Four of the deaths were related to the route of microbiota administration and the aspiration of the transplanted material. One death resulted from a blood infection caused by a drug-resistant strain of E. coli, the source of which was FMT. The majority of deaths related to FMT could have been prevented by considering and mitigating the risks associated with the route of transplant administration. The risk of death due to microbiota was estimated at 0.02% (1/4241 cases).

4.9.4 Adverse reactions depending on the route of transplant administration

The incidence of adverse reactions from FMT varied depending on the route of transplant administration used (Figure 1). Adverse reactions were more common in patients who received FMT through the upper gastrointestinal tract (28.8%) compared to those who received FMT via the lower gastrointestinal tract (17.5%). The incidence of serious adverse reactions was 1.4% and 0.9% for FMT administered via the upper and lower gastrointestinal tract, respectively.

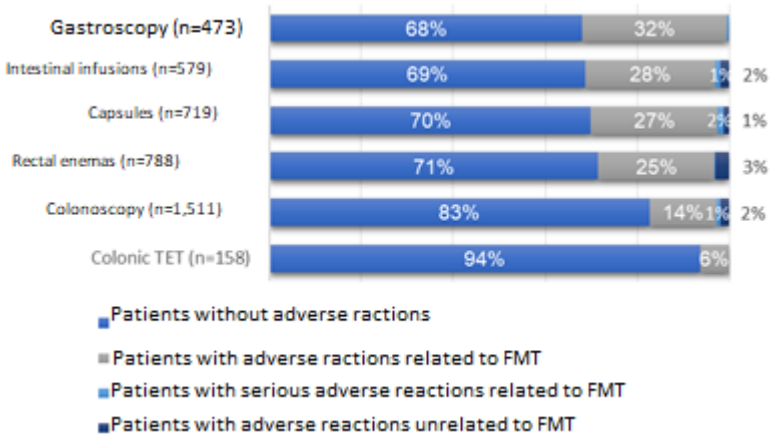

Figure 1. Incidence of adverse reactions from FMT depending on the route of administration. The incidence of adverse reactions is lowest with rectal enema (Colonic TET) and highest with gastroscopy.

When FMT was administered via duodenal/gastric/enteric tubes, all serious adverse reactions were related to the route of administration. Therefore, necessary precautions for procedures involving administration of FMT through the upper gastrointestinal tract must include preventing the reflux of the transplanted contents, maintaining an upright position during FMT administration, and adjusting the infusion rate to optimal tolerability.

4.9.5 Adverse reactions depending on the indication for transplantation

Based on additional data provided by the review authors, an analysis was conducted on the incidence of adverse reactions in patients with infections caused by antibiotic-resistant bacteria (including C. *difficile*). The overall incidence of adverse reactions, the incidence of serious adverse reactions, and deaths were analysed. Table 2. shows the results of the analysis.

Table 2. Incidence of adverse reactions and deaths depending on the indication for FMT. The incidences of adverse reactions overall are provided, without considering cause-effect relationships.

	Patients with adverse reactions, n (%)	Patients with serious adverse reactions, n (%)	Deaths, n (%)
Antibiotic-resistant bacteria infections (n=48)	34 (50.8%)	7 (14.6%)	6 (17.6%)
C. *difficile* infections (n=2,654)	631 (27.6%)	163 (7.1%)	92 (4.0%)
Ulcerative colitis (N=590)	217 (36.8%)	13 (2.2%)	0 (0%)
Crohn disease (n=211)	67 (31.7%)	0 (0%)	0 (0%)

*- the analysis also included studies in which infections were accompanied by other somatic diseases

The overall incidence of adverse reactions was higher for each of the FMT indications analysed than that observed in the general population of recipients. FMT in patients with antibiotic-resistant bacteria infections was associated with a higher incidence of serious adverse reactions and deaths compared to the other patient groups analysed. The majority of serious adverse reactions and deaths occurred in critically ill patients who received FMT (case report series by Dai et al., 2019). None of the deaths were classified as related to FMT.

4.9.6 Reporting suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via Pharmacovigilance Department of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (despite the lack of appropriate regulations in Poland); *Al. Jerozolimskie 181C 02-222 Warszawa* Tel.: + 48 22 49 21 301; fax: + 48 22 49 21 309;

website: https://smz.ezdrowie.gov.pl

Adverse reactions should also be reported to the Marketing Authorisation Holder (Human Biome SA).

4.10 Overdose

No case of overdose has been described. Gut microbiota preparations are used in different does and volumes.

5. Pharmacological properties

Not applicable

5.1 Pharmacodynamic properties

Not applicable

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

Similar safety data has been reported in preclinical and clinal studies – see section 4.9.

6. Pharmaceutical particulars

6.1 List of excipients

Syringe kit: 0.9% NaCl, pharmaceutical glycerine

Capsules: 0.9% NaCl, pharmaceutical glycerine, hypromellose, gellan gum, titanium dioxide, hypromellose AS

6.2 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

6.3 Shelf life

Products can be stored at -80°C for up to 3 years

At the temperature of -20°C, products can be stored for no longer than 3 months

6.4 Special precautions for storage

Defrosted product is not suitable for refrosting.

6.5 Nature and contents of container

Syringe kit:
Carton containing two syringes for single administration.

Capsule set:
Carton containing 6 jars.

6.6 Special precautions for disposal and preparation of the product for use

The preparation in the form of suspension must be defrosted 4 - 5 hours before the scheduled procedure. MBiotix® HBI syringe kit requires no special methods of defrosting. The preparation should be removed from the freezer and left in the open box until defrosted. Each syringe is sealed with a cap to prevent leakage of the product. The average defrosting time is between 4 and 5 hours. The syringe with the preparation should be shaken and inverted several times before use. The preparation must not be used if there are contaminants in the suspension.

MBiotix® HBI Caps must be frozen at the time of administration. Defrosted product is not suitable for administration.

Unused products or their waste should be disposed of in accordance with local regulations.

7. Marketing authorisation holder

HUMAN BIOME S.A.
1 Starodworska street,
80-137 Gdańsk
Tax Identification Number: 583-338-47-60

8. Marketing authorisation number

Not applicable

9. Date of first authorisation/renewal of the authorisation

Not applicable

10. Date of approval/partial revision of the text

01/01/2023