AUSTRALIAN PRODUCT INFORMATION – BIOMICTRA (FAECAL MICROBIOTA TRANSPLANTATION)

1 NAME OF THE MEDICINE

Biomictra Faecal Microbiota

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Biomictra FMT syringe contain 12.5g of faecal microbiota as the active ingredient.

Biomictra FMT is comprised of human donor stool (faecal microbiota) 12.5 g (25%), sodium chloride (0.9%) 32.5 ml (65%) and glycerol 5 mL (10%) Human donor stool contains a large number of micro-organisms including bacteria, fungi, archea, protozoa and viruses including phage. Human donor stool also contains food from the donor's diet and a small quantity of cells from the donor's colon. The composition of each FMT preparation will vary in composition. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Biomictra FMT syringes are clear, polypropylene 60 mL syringes, sealed using a plastic bumper.

The Biomictra syringe contains 50 mL of a brown-coloured suspension.

4 CLINICAL PARTICULARS

4.1 INTENDED USE

Biomictra is for the restoration of the gut microbiota in the management of gastrointestinal disorders.

Conditions of registration:

- Product must only be provided for use by a medical practitioner registered in an Australian State or Territory, under the supervision or on the advice of a specialist gastroenterologist or infectious diseases physician; and
- Product must not be released for use in conditions other than *C. difficile* infection, unless as part of a registered clinical trial or via the Special Access Scheme or via Authorised Prescriber Scheme.
- Data of real-world clinical efficacy for product released after up to 12 months storage compared to product released after 12-24 months storage must be collected over the next 18 months. The sponsor must advise TGA as soon as possible of any adverse data. Reports must be provided to the TGA via self-assessable variation submission for review after 9 months data collection and after 18 months data collection (with the first report with 9 months data due in October 2024 and the second in June 2025).

Use should be guided by clinical trial evidence, national and international guidelines and society position statements on the use of FMT.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administration of Biomictra syringes is at the discretion of the medical provider and will be influenced by particular patient factors and clinical practice guidelines.

The evidence for colonoscopic delivery of FMT is greater than for other delivery methods. Colonoscopic delivery of FMT should be the first preference, however for patients with contraindications to colonoscopy or who are frail, other methods such as enema or upper gastrointestinal delivery can be used. All supplied treatments of Biomictra are single patient use and are not to be mixed with another batch.

Colonoscopic delivery

1. Remove Biomictra packet from -80°C freezer and thaw for 4 hours at room temperature (or 10 hours at 4°C) prior to procedure.
2. Record FMT batch number and date of production in patient's medical record.
3. Record patient's name, UR number, date of birth, date of first CDI, number of relapses in prospective database (if established)
4. Prior to positioning patient for procedure, ideally place a sliding sheet under the normal sheet to assist rolling the patient during the procedure.
5. All proceduralists and assistants should be wearing a mask and splash shield or protective eyewear prior to FMT administration.
6. During the colonoscopy, suction as much residual stool and fluid as possible from the colon on entry.
7. Once the scope reaches the caecum, using the sliding sheet roll the patient onto their right side.
8. Cover patient, bed rails and any nearby surfaces with towels or absorbent sheets to contain any spillage.
9. Delivering Biomictra:
    - Remove the colonoscopy biopsy valve and insert the syringe into the biopsy port
    - Flush the FMT into the channel
    - Once syringe is empty, place finger over biopsy port while swapping syringes to prevent spillage
    - Repeat until all syringes have been used
    - Using one of the empty syringes, draw up 30 mL of sterile water for injection and flush the biopsy channel
10. Withdraw the scope without suctioning
11. Patient to remain in right lateral position for at least 1-hour post FMT administration before getting up
12. Encourage high fibre diet and inform patient that antibiotics pose a risk of relapse of CDI in future

Enema delivery

1. Remove Biomictra enema syringe from -80°C freezer and thaw for 4 hours at room temperature (or 10 hours at 4°C)
2. Record patient's name, UR number, date of birth, date of first CDI, number of relapses in prospective database (if established)
3. Record stool aliquot code and date of production in patient's medical record.
4. Ask patient to empty bowels prior to FMT administration
5. Position patient in left lateral position with knees drawn up on bed in close proximity to a toilet or commode with a towel and absorbent sheet placed under their bottom

6. All proceduralists and assistants should be wearing a mask and splash shield or protective eyewear prior to FMT administration
7. Delivering Biomictra enema:
    - Add some lubricant to the perianal area and lubricate the tip of the syringe
    - A rectal applicator may need to be used to aid administration
    - Gently introduce the tip of the syringe as far as possible into the rectum
    - Warn the patient that the FMT may be cold and can cause some discomfort
    - Slowly deploy the plunger to deliver FMT into rectum
8. Roll patient into the prone position with a pillow under their hips to help retain the enema for 30 mins
9. Instruct patient to delay defaecation for as long as able

Upper GI delivery

1. Remove 2 x Biomictra Syringes from -80°C freezer and thaw for 4 hours at room temperature (or 10 hours at 4°C) prior to procedure
2. Record patient's name, UR number, date of birth, date of first CDI, number of relapses in prospective database (if established)
3. Record stool aliquot code and date of production in patient's medical record
4. All proceduralists and assistants should be wearing a mask and splash shield or protective eyewear prior to FMT administration
5. Perform a push enteroscopy, aiming for the jejunum
6. Cover the patient, bed sides and any nearby surfaces with towels or absorbent sheets to contain any spillage
7. Position patient with head elevated to approximately 30 degrees
8. Delivering Biomictra:
    - Remove the biopsy valve and insert the syringe into the biopsy port
    - Flush the FMT into the channel
    - Once syringe empty, place finger over biopsy port while swapping syringes to prevent spillage
    - Repeat until both syringes have been used
    - Using one of the empty syringes, draw up 30 mL of sterile water for injection and flush the biopsy channel
9. Withdraw the scope without suctioning in the small bowel
10. On withdrawing the scope, make sure the tip and the channel are not contaminated with FMT to prevent introducing FMT into the stomach or oesophagus to prevent aspiration. If concerned, flush channel or suction away from where the FMT was introduced.
11. If patient experiences any nausea, treat immediately with anti-emetics to prevent aspiration

4.3 CONTRAINDICATIONS

1. Suspected bowel perforation
2. Anaphylactic food allergy. Biomictra contains food antigen from the donor's diet and so could induce anaphylaxis in a recipient who was susceptible

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Donors are thoroughly screened using a medical history, physical examination as well as blood and stool testing. This minimises the risk of disease transmission from stool donor to recipient, however some risk remains.

Cytomegalovirus (CMV) and Epstein Barr Virus (EBV): Donors may have been exposed to CMV and EBV in the past and so it is important for the treating clinician to weigh the risk of primary CMV or EBV infection for the recipient of FMT against the risk of the disease being treated. This may be particularly important in recipients who are immunocompromised and patients should be counselled and consented regarding these risks. There have been at least 6 cases of CMV infection in FMT recipients documented in the literature and it is possible, that in some of these cases CMV may have been transmitted by FMT. There have not been any confirmed reports of EBV transmission in the literature to date.

Immunocompromised Patients

Immunocompromised patients are at a theoretical increased risk of some infections from FMT, however cohort and case control studies have not demonstrated a significantly increased risk from FMT in this population relative to non-immune suppressed populations.

In patients where there is a loss of the gastrointestinal mucosal integrity there may be a higher risk of bacterial translocation into the patient's bloodstream. There have been case reports of this occurring.

Latent infection with herpes viruses including cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus 1 and 2, varicella zoster virus and human herpes viruses 6 and 8 can be present in the donor and asymptomatic mucosal shedding could occur.

BiomeBank can provide FMT from a CMV seronegative donor for a CMV seronegative immunocompromised recipient on request.

Use in hepatic impairment Limited data supports the safe use of FMT in patients with hepatic impairment.

Use in renal impairment FMT can be used in patients with renal impairment.

Use in the elderly: FMT can be used safely in elderly patients. The mode of delivery may be influenced by co-morbidities and the age of the patient and this should be assessed by the treating physician.

Paediatric use: There is very limited data on use of FMT in the paediatric population. An individual assessment of risk and benefit is advised. Long term effects are unknown.

Effects on laboratory tests: No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Antibiotics following FMT therapy are the most frequent association with FMT treatment failure in the treatment of *C. difficile* infection.

Very limited data are available on the effect of FMT on other medicines. There are case reports of FMT augmenting the efficacy of check point inhibitor therapies for the treatment of

some malignancies. A number of medicines are metabolised in part by gut bacteria and hence changes in gut bacteria with FMT may theoretically alter the pharmacokinetics of the medicine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility: No data available

Use in pregnancy

There is limited data on the use of FMT in pregnancy

Use in lactation

No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should not drive or operate machinery after sedation or anaesthetic for colonoscopy associated with administration however, Biomictra FMT does not cause sedation or impair the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

FMT may have unwanted side effects in some people.

Approximately 19% of people experience an adverse event following FMT. Minor adverse events such as transient diarrhoea, abdominal discomfort or nausea are common. Approximately 1.3% of patients may experience a serious adverse event following FMT. Most research on FMT has occurred in the last 10 years. There is limited data on the long-term risks of FMT.

Colonoscopic delivery of FMT has a lower rate of adverse events relative to enema, upper gut delivery or capsule delivery of FMT.

Risks of FMT

Abdominal symptoms. Transient symptoms of abdominal bloating or discomfort are possible following FMT and can occur in up to 20% of patients.

Up to 12% of patients experience a post infectious irritable bowel syndrome following successful eradication of *Clostridioides difficile* infection with symptoms of abdominal bloating or discomfort and diarrhoea that may take weeks or potentially months to resolve.

Transmission of infection. There have been cases of confirmed bacterial infection from stool donor to FMT recipient.

Infections caused by Enteropathogenic *E. coli* (EPEC), Shiga toxin-producing E. coli (STEC) and the multidrug resistant organism extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli have occurred following use of FMT. Cases of CMV and Norovirus infections in FMT recipients have been reported.

There have been deaths related to treatment with FMT including from infection and procedural complications.

Transmission of other conditions. There is an association between some medical conditions such as obesity and certain gut bacterial profiles. It is possible that the gut microbiome may contribute to other diseases that may be transmitted via FMT. Therefore, there are unknown

risks associated with the use of FMT. Donors are screened for any medical condition and family history of medical conditions that could potentially impact on the FMT recipient.

Allergy. There is a small risk of an allergic reaction after receiving FMT. Biomictra FMT may contain nuts and other food residue and so patients with anaphylactic food allergy should not take Biomictra FMT.

Procedure related risks

FMT is often administered by colonoscopy.

The major risk of colonoscopy is bowel perforation, which occurs in less than 1 in 1000 colonoscopies.

Other risks of colonoscopy include dehydration from bowel preparation, over-sedation, aspiration, bleeding and splenic laceration. Some biopsies may be taken during this procedure. Taking biopsies has a very small (less than 1:1000) risk of relevant bleeding. If you are on strong blood thinning medication (e.g., Warfarin), or have a bleeding disorder, the risk of bleeding may be greater.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the biological product is important. It allows continued monitoring of the benefit-risk balance of the biological product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.
Any concern regarding an adverse event associated with donor stool for FMT must be reported to BiomeBank as soon as it is detected. Any potential adverse events can be discussed with a member of the BiomeBank team by phone (08 81528370) or email: safety@biomebank.com

Prospective Database: We recommend each hospital maintain a prospective database of patients who receive FMT. BiomeBank can provide such a database should institutions want this.

To ensure adequate traceability and monitoring of the safety and efficacy of the BiomeBank's FMT products, the administering physician must complete a follow up form 8 weeks after administration. This is provided with all shipments." **Product Complaint / Return Policy**

Product complaint (issues with packaging, labelling, syringe) should be reported as soon as possible to the BiomeBank Quality team by phone (08 81528370) or email: quality@biomebank.com

BiomeBank cannot accept return of Biomictra as it is a biological product. If there are any problems with the product a staff member will provide you with instructions on how to discard the product.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 BIOLOGICAL PROPERTIES

5.1 BIODYNAMIC PROPERTIES

Mechanism of action

For restoration of the gut microbiome. Current evidence suggests that FMT works via restoration of gut microbial diversity

Clinical trials

A systematic literature review and meta-analysis assessed the overall efficacy of FMT in treating recurrent *Clostridioides difficile* infection (rCDI, defined as one or more *C. difficile* infections), the effect of delivery method and treatment regimen on efficacy, and compared FMT with standard antibiotics. Clinical effect week 8 following repeat FMT (24 studies, 1855 patients) was 91% (95% CI: 89-94%, I^2=53%) and 84% (80-88%, I^2 = 86%) following single FMT (43 studies, 2937 patients). Delivery by colonoscopy was superior to all other delivery methods. Compared with vancomycin, the number needed to treat (4 randomised controlled trials, 151 patients) for repeat FMT to effect one cure was 1.5 (1.3-1.9, P<0.001)[1] and for single FMT was 2.9 (1.5 – 37.1, P = 0.03).

5.2 BIOKINETIC PROPERTIES

The donated microbiota stays compartmentalized in the gastrointestinal tract; it is not distributed to other organs in the body. The donor microbiota partially engrafts. This process is shaped by interactions with pre-existing and subsequent microbiota constituents, as well as by the host immune system and diet.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium chloride

Glycerol

6.2 INCOMPATIBILITIES

Refer to Section 4.5 Interactions with other medicines

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

a. Biomictra syringes should be stored between -90°C & -70°C in a dedicated compartment of the freezer. No other material should be stored in this

compartment of the freezer.

b. Biomictra syringes can be stored for 24 months from the date of manufacture at -80°C. The listed expiry date is for storage at -80°C only.
c. Appropriate gloves should be used during transfer of Biomictra product as it is cold and submerged in dry ice during transport.
d. The freezer should be labelled as containing FMT treatment product.

6.5 NATURE AND CONTENTS OF CONTAINER

Biomictra FMT syringes are clear, polypropylene 60 mL syringes, sealed using a plastic bumper. The Biomictra syringe contains 50 mL of a brown-coloured suspension.

Biomictra syringes are supplied as a pack containing either one or four 60 mL Biomictra pre-filled syringes.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused Biomictra FMT syringes or waste material should be disposed of in a biological waste bin or facility.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not applicable

8 SPONSOR

BiomeBank

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https://biomebank.com

9 DATE OF FIRST APPROVAL

9 November 2022

10 DATE OF REVISION

13 October 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New PI for FMT
4.1	Included update to specific conditions – use via Special Access Scheme or via Authorised Prescriber Scheme
4.1 & 6.4	Included update to conditions of registration and special precautions for storage – 24 months shelf-life