ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

NULIBRY 9.5 mg powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 12.5 mg fosdenopterin hydrobromide dihydrate equivalent to 9.5 mg fosdenopterin.

After reconstitution with 5 mL of sterile water for injections, each mL of solution contains 1.9 mg of fosdenopterin (1.9 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

White to pale yellow powder.

The reconstituted solution has a pH in the range of 5-7, a viscosity of 1.0 cSt, and an osmolarity within the range of 260-320 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NULIBRY is indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.

4.2 Posology and method of administration

NULIBRY is to be administered only if the patient has a confirmed genetic diagnosis or presumptive diagnosis of MoCD Type A.

Patients with a presumptive diagnosis of MoCD Type A need to have a genetic test to confirm the diagnosis of MoCD Type A. NULIBRY must be discontinued if the MoCD Type A diagnosis is not confirmed by genetic testing.

Treatment with NULIBRY is to be initiated and supervised in hospital by a healthcare professional experienced in the management of inborn errors of metabolism. NULIBRY is a chronic substrate replacement therapy intended for long-term use.

Posology

Paediatric population less than 1 year of age (by gestational age)
In patients less than one year of age, the recommended dose of NULIBRY is titrated based on gestational age.

For patients less than 1 year of age who are preterm neonates (gestational age < 37 weeks), the recommended starting dose of NULIBRY is 0.40 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months as shown in Table 1.

For patients less than 1 year of age who are term neonates (gestational age ≥ 37 weeks), the recommended starting dose of NULIBRY is 0.55 mg/kg/day administered intravenously once daily. The dose is to be titrated to the target dose of 0.90 mg/kg/day over a period of 3 months as shown in Table 1.

Table 1 Starting dose and titration schedule of NULIBRY for patients less than one year of age by gestational age

Titration schedule	Preterm neonate (gestational age less than 37 weeks)	Term neonate (gestational age 37 weeks and above)
Initial dose	0.40 mg/kg once daily	0.55 mg/kg once daily
Dose at month 1	0.70 mg/kg once daily	0.75 mg/kg once daily
Dose at month 3	0.90 mg/kg once daily	0.90 mg/kg once daily

Paediatric population from 1 year to less than 18 years of age and adults
The recommended dose of NULIBRY is 0.90 mg/kg (based on actual body weight) administered intravenously once daily.

Missed dose
If a dose is missed, the missed dose is to be administered as soon as possible. The next scheduled dose must be given at least 6 hours after the administration of the missed dose.

Method of administration

NULIBRY is for intravenous use only.

NULIBRY is intended for administration at an infusion rate of 1.5 mL/min after reconstitution with 5 mL of sterile water for injection. Dose volumes below 2 mL may require syringe administration by slow intravenous push.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

If deemed appropriate by a healthcare professional, NULIBRY may be administered at home by the patient's caregiver. If NULIBRY is administered by a caregiver/patient, the caregiver/patient must read and follow carefully the detailed "Instructions for the user" on the preparation, administration, storage, and disposal of NULIBRY provided in the carton.

The healthcare professional should calculate and provide the volume of NULIBRY in millilitres (mL) and the number of vials needed for each dose to the caregiver/patient, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Potential for photosensitivity

Photosensitivity is a potential risk based on *in vitro* and *in vivo* animal studies, see section 5.3.

Fosdenopterin-treated patients or their caregivers must be advised that patients avoid or minimise exposure to direct sunlight and artificial UV light exposure (i.e., UVA or UVB phototherapy) and adopt precautionary measures (e.g., use broad spectrum sunscreen with high sun protection factor, and wear clothing, a hat, and sunglasses that protects against sun exposure). Caregivers/patients must be advised to seek medical attention immediately if the patient develops a rash or if they notice symptoms of photosensitivity reactions (redness, burning sensation of the skin, blisters). Physicians should consider Vitamin D supplementation due to the use of sunscreens and sun protective clothing and advise the caregiver/patients accordingly.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug-drug interaction studies have been performed with fosdenopterin.

The likelihood of metabolism-based and transporter-based drug-drug interactions with fosdenopterin are minimal, and co-administration of other medicinal products is not likely to affect the pharmacokinetics of fosdenopterin (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of fosdenopterin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

NULIBRY is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

It is unknown whether fosdenopterin/metabolites are excreted in human milk.

A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue from NULIBRY therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility studies have not been conducted with fosdenopterin.

4.7 Effects on ability to drive and use machines

NULIBRY has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The adverse drug reactions described in this section were evaluated in 11 patients with MoCD Type A. The most frequent (> 20%) adverse reaction observed during clinical trials were complications

associated with device, which have been attributed to the catheter and not to fosdenopterin. No patients had to have their treatment discontinued due to adverse events.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) observed are listed below by MedDRA system organ class and by frequency: 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 available data).

Table 2 presents the most common ADRs that occurred in patients treated with NULIBRY.

Table 2 Adverse reactions reported by SOC/PT and frequency

System Organ Class	Very common (≥ 10%)
General disorders and administration site conditions	Complications associated with device

Description of selected adverse reactions

Catheter-related complications
Eight of ten patients treated with NULIBRY experienced at least one device-related adverse event. The events reported in more than one patient included complications associated with device (7 patients), device dislocation and catheter site infection (3 patients each), and catheter site extravasation, catheter site pain, central venous catheterization, catheter site discharge, device leakage, device occlusion, bacteraemia, sepsis, and vascular device infection (2 patients each).

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 listed in Appendix V.

4.9 Overdose

The maximum tolerated dose of NULIBRY has not been established, and there is no known antidote for fosdenopterin. In the event a patient receives a dose of NULIBRY greater than the intended dose, frequent monitoring of vital signs and clinical status is recommended for a minimum of 8 hours after dosing.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, various alimentary tract and metabolism products; ATC code: A16AX19

Mechanism of action

Patients with MoCD Type A have mutations in the Molybdenum Cofactor Synthesis 1 (MOCS1) gene leading to deficient MOCS1A/B dependent synthesis of the intermediate substrate, cPMP. Substrate replacement therapy with NULIBRY provides an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including sulphite oxidase (SOX), an enzyme that reduces levels of neurotoxic sulphites.

Clinical efficacy and safety

The efficacy of NULIBRY and rcPMP was assessed in a combined analysis of the 15 patients with genetically confirmed MoCD Type A who received substrate replacement therapy with NULIBRY and/or rcPMP, which has the same active moiety as fosdenopterin and is considered therapeutically equivalent as NULIBRY.

Of the 15 treated patients included in the combined analysis, 47% were male, 73% were white and 27% were Asian; the median gestational age was 39 weeks (range 35 to 41 weeks). Median age at genetic diagnosis was 4 days across the 15 patients and included 6 patients with a prenatal diagnosis.

Overall survival is presented in Table 3.

Table 3 Overall survival in patients with MoCD type A treated with NULIBRY or rcPMP

	NULIBRY (or rcPMP) (n=15)
Number of deaths (%)	2 (13.3%)
Kaplan Meier survival probability 1 year 3 years	 93% 86%
Mean survival time (months) (Median; Min, Max)	73.2 (64.4; 0, 162)

Abbreviations: CI=confidence interval; rcPMP=recombinant Escherichia coli derived cPMP.

Findings from the overall survival analysis were compared with an untreated natural history control group. Overall survival was significantly prolonged in patients who received NULIBRY compared to the untreated natural history control group.

Compared to the untreated natural history group, patients who received NULIBRY were more likely to be ambulatory, feed orally, gain weight, progress developmentally, and attain a head circumference closer to their age matched peers. Neurological damage that occurred prior to therapy, including in utero, is not reversible.

MoCD urinary biomarkers
Treatment with NULIBRY resulted in a reduction in urine concentrations of S-sulfocysteine (SSC) in patients with MoCD Type A and the reduction was sustained with long-term treatment over 48 months. The baseline level of urinary SSC normalised to creatinine was characterised in two patients with a mean value of 92.0 µmol/mmol. Following treatment with NULIBRY (n=15), the mean ± SD levels of urinary SSC normalised to creatinine ranged from 12.9 (±7.3) to 8.6 (±5.8) µmol/mmol from Month 3 to the last visit.

Adolescent and adult population

There are limited data in adolescents ages 12 to less than 18 years of age and adults.

Exceptional circumstances

This medicinal product has been authorised under ‘exceptional circumstances’. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.
The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of fosdenopterin in healthy adult subjects following a single intravenous administration of fosdenopterin are summarised in Table 4. The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of fosdenopterin increased in an approximately proportional manner with increasing doses.

Table 4 Mean (SD) pharmacokinetic parameters following a single intravenous dose of fosdenopterin in healthy subjects

Parameter	0.075 mg/kg[1]	0.24 mg/kg[1]	0.68 mg/kg[1]
C_{max} (ng/mL)	285 (57)	873 (99)	2800 (567)
$AUC_{0\text{-}inf}$ (ng*h/mL)	523 (75)	1790 (213)	5960 (1820)

[1] 0.075 mg/kg, 0.24 mg/kg, and 0.68 mg/kg doses are 0.08, 0.27, and 0.76 times the recommended maximum dose, respectively.

Distribution

The volume of distribution (Vd) of fosdenopterin was approximately 300 mL/kg. The plasma protein binding of fosdenopterin ranged from 6 to 12%.

Biotransformation

Fosdenopterin is predominantly metabolised through nonenzymatic degradation processes to an inactive oxidation product of endogenous cPMP.

Investigation of potential for drug interaction
The potential for drug-drug interactions based on cytochrome P450 (CYP) and/or transporter interactions was studied in a number of *in vitro* studies.

Fosdenopterin does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5 isozymes when tested *in vitro* in human liver microsomes. There was little or no direct time-dependent or metabolism-dependent inhibition of these isozymes, and the half maximal inhibitory concentration (IC_{50}) values were reported as > 500 µM. Fosdenopterin did not demonstrate induction of CYP1A2, CYP2B6, or CYP3A4. Treatment of cultured human hepatocytes with up to 100 µM fosdenopterin produced little or no increase in CYP1A2, CYP2B6, or CYP3A4 mRNA and enzyme activity levels.

Fosdenopterin does not inhibit efflux or uptake transporters. Inhibition of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 (20 µM), OAT3, MATE1, and MATE2-K (20 µM) was reported as < 10% at 200 µM, while cPMP demonstrated slight inhibition of MATE2-K (25%) and OAT1 (33%) at 200 µM. Fosdenopterin is not a substrate of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, or MATE2-K, and is possibly a weak substrate for MATE1.

Elimination

The mean total body clearance (CL) of fosdenopterin ranged from 167 to 195 mL/h/kg. The mean half-life of fosdenopterin ranged from 1.2 to 1.7 hours.

Renal clearance of fosdenopterin accounts for approximately 40% of total body clearance.

Specific populations

Studies have not been conducted to evaluate the pharmacokinetics of fosdenopterin in specific patient populations, identified by race, age, or the presence of renal or hepatic impairment. The effect of renal and hepatic impairment on the pharmacokinetics of fosdenopterin is unknown.

Paediatric population

Pharmacokinetic properties of fosdenopterin in paediatric MoCD Type A patients are similar to healthy adult subjects.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity in juvenile animals, and genotoxicity.

Carcinogenicity

Carcinogenicity studies have not been conducted with fosdenopterin.

Reproductive and developmental toxicity

Reproductive and developmental toxicity studies have not been conducted with fosdenopterin.

Phototoxicity

Fosdenopterin was phototoxic *in vitro* and *in vivo*. In rats, cutaneous skin reactions (erythema, oedema, flaking, and eschar) and ophthalmic and histopathologic changes were observed after UV radiation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ascorbic acid (E300)
Mannitol (E421)
Sucrose
Hydrochloric acid (E507) (for pH adjustment)
Sodium hydroxide (E524) (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

2 years

After reconstitution

Reconstituted NULIBRY may be stored at room temperature (15 °C to 25 °C) or refrigerated (2 °C to 8 °C) for up to 4 hours including infusion time. Do not freeze NULIBRY after reconstitution. Do not shake.

Chemical and physical in-use stability has been demonstrated for 4 hours at 2 °C to 8 °C or 15 °C to 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than the above mentioned conditions when reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Unopened vial

Store in a freezer at -25 °C to -10 °C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL type I clear glass vial with an aluminium seal and butyl rubber stopper.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only and the excess of unused product must be properly disposed. Sterile water for injection, syringes, needle tips, and alcohol wipes are to be provided to the patient.

Reconstitution

NULIBRY must be reconstituted with 5 mL of sterile water for injections prior to use. Reconstituted NULIBRY must not be shaken nor heated. Aseptic technique is to be used during preparation and these instructions are to be followed:

1. The total dose, number of vials needed, and total reconstituted dose volume based on the patient's weight and prescribed dose must be determined. Dose volumes can range from 0.4 mL for a 2 kg preterm neonate (0.40 mg/kg/day) to 23.7 mL for a 50 kg adult (0.90 mg/kg/day). See section 4.2. Number of vials to be reconstituted is determined by patient’s dose divided by 9.5 mg/vial (content of one vial). If the number of calculated vials includes a fraction, it should be rounded up to the next whole number.

2. The required number of vials is to be removed from the freezer to allow them to reach room temperature (by rolling each vial gently between your hands for 3 to 5 minutes (do not shake) or by leaving it at room temperature for approximately 30 minutes).

3. Each required NULIBRY vial must be reconstituted with 5 mL of sterile water for injections. Each vial is reconstituted by slowly injecting 5 mL of water for injections to the inside of the wall of each vial. The vial must be gently and continuously swirled until the powder is completely dissolved. The vial must not be shaken. After reconstitution, the final concentration of NULIBRY reconstituted solution is 9.5 mg/5 mL (1.9 mg/mL). Only the volume corresponding to the recommended dose should be administered.

4. Reconstituted NULIBRY is a clear and colourless to pale yellow solution. NULIBRY is to be visually inspected for particulate matter and discoloration prior to administration. NULIBRY must not be used if there are particles present or if the solution is discoloured.

5. The total reconstituted dose is to be administered.

If reconstituted NULIBRY is refrigerated, allow it to come to room temperature before administration by rolling each vial gently between your hands 3 to 5 minutes (do not shake) or by leaving it at room temperature for approximately 30 minutes.

Administration

NULIBRY is intended for administration by a healthcare professional. If deemed appropriate by a healthcare professional, NULIBRY may be administered at home by the patient's caregiver (see section 4.2). If NULIBRY can be administered by a caregiver/patient, caregiver/patient must read the detailed instructions on the preparation, administration, storage, and disposal of NULIBRY.

NULIBRY is for intravenous use only. NULIBRY must be administered with di(2-ethylhexyl)phthalate (DEHP)-free tubing with a 0.2 micron filter. NULIBRY must not be mixed with other medicinal products (note NULIBRY is reconstituted with sterile water for injections). NULIBRY must not be administered as an infusion with other medicinal products.

NULIBRY is given through a syringe pump at a rate of 1.5 mL per minute.

Dose volumes below 2 mL may require syringe administration through slow intravenous push.

Administration of NULIBRY must be completed within 4 hours of reconstitution.

Disposal of medicinal product and auxiliary components

Any unused medicinal product or waste material including materials used for reconstitution and administration should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TMC Pharma (EU) Ltd
G24A Arc Labs Research and Innovation Centre,
SETU West Campus, Carriganore,
Waterford, X91 P20H,
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1684/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15-09-2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Sciensus International B.V.
Bijsterhuizen 3142
6604 LV Wijchen,
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of NULIBRY in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational material is aimed at minimising medication errors.

The MAH shall ensure that in each Member State where NULIBRY is marketed, all patients/caregivers who are expected to use NULIBRY in home setting are provided with the following educational material to be disseminated through healthcare professional:

- Instructions for use

- Infusion Diary

Instructions for use:
- Important information patient/caregiver need to know before preparing and giving NULIBRY;
- Instructions on the time over which the product should be administered;
- A description of the diluent for reconstitution;
- The administration time required after reconstitution;
- Step by step instructions (with visuals for the majority of the steps, and typeface and white space).

Infusion Diary:
- It should function also as a communication tool between the physician, the patient, and the caregiver to monitor safety and additional risk minimisation measures.
- This document will contain items including
    - emergency contact numbers,
    - the prescribed dose and regimen provided by the treating physician,
    - a record of the drug administration by the caregiver including dates, doses administered, adverse events, medication errors, and administration complications in the home setting.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to ensure adequate monitoring of safety and efficacy of Nulibry in the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Nulibry.	Annually (with annual re-assessment)
Non-interventional Post authorisation safety study (PASS): In order to further characterise the long-term safety and efficacy of Nulibry, the MAH should conduct and submit the results of an observational, prospective study of patients with molybdenum cofactor deficiency (MoCD) Type A treated with Nulibry.	Annually (with annual re-assessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

NULIBRY 9.5 mg powder for solution for injection
fosdenopterin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains fosdenopterin hydrobromide dihydrate equivalent to 9.5 mg fosdenopterin. After reconstitution with 5 mL of sterile water for injections, each mL of concentrate contains fosdenopterin hydrobromide dihydrate equivalent to 1.9 mg fosdenopterin.

3. LIST OF EXCIPIENTS

Excipients: ascorbic acid, mannitol, sucrose, hydrochloric acid, sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a freezer at -25 °C to -10 °C
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TMC Pharma (EU) Ltd

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1684/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille requested.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NULIBRY 9.5 mg powder for injection
fosdenopterin
IV use after reconstitution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

9.5 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NULIBRY 9.5 mg powder for solution for injection.
fosdenopterin

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you or your child.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you or your child get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NULIBRY is and what it is used for

What NULIBRY is
NULIBRY contains the active substance fosdenopterin.
NULIBRY is given to people with the genetic disease molybdenum cofactor deficiency (MoCD) Type A. It is given to people when doctors suspect that they might have MoCD Type A. It needs to be continued for life if MoCD Type A is confirmed by genetic testing.

What molybdenum cofactor deficiency (MoCD) Type A is
MoCD Type A is a rare inborn error of the natural chemical processes needed for your body to work (metabolism). Signs of this genetic disease usually appear shortly after birth and include difficulty feeding and seizures. Other signs are a decreased awareness or reaction to the environment, an increase in startle reactions to a sudden event, and weak or stiff muscles.

MoCD type A results from an error in the gene called MOCS1. This stops the body from making an essential substance called cyclic pyranopterin monophosphate. When this substance is missing, certain compounds (sulphites) formed in the body cannot be broken down. These compounds are toxic to the brain and can negatively affect or delay the development of a child.

How NULIBRY works
NULIBRY provides the missing substance that you or your child's body needs to break down the harmful sulphite compounds.

2. What you need to know before you use NULIBRY

Do not use NULIBRY
- if you or your child is allergic to fosdenopterin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before using NULIBRY.

Patients who use NULIBRY may become sensitive to direct sunlight and ultraviolet light. During treatment with fosdenopterin, patients should avoid exposure to sunlight, and wear sunscreen, protective clothing, and sunglasses when exposed to the sun. Tell your doctor immediately if you or your child develops a rash, redness or blisters on sun-exposed areas of the skin, or if you or your child experience a burning sensation of the skin.

Due to the use of sunscreens and sun protective clothing your doctor may prescribe additional vitamin D as necessary.

Other medicines and NULIBRY
It is unlikely that NULIBRY has an influence on or is influenced by other medicines. However, tell your doctor if your child is taking, has recently taken, or might take any other medicines.

NULIBRY contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How to use NULIBRY

How NULIBRY is given
NULIBRY is injected into a vein through a catheter.

A doctor who is experienced in the management of inborn errors of metabolism will start and supervise the treatment with NULIBRY.

NULIBRY can be given at home. Before you do this for the first time, your doctor or nurse will train you in how to prepare the medicine and give you or your child a dose of NULIBRY.

Always use this medicine exactly as your doctor or nurse has instructed. Check with your doctor if you or your child are not sure about how to use NULIBRY.

How much to use
The dose depends on your child's age and body weight. You will need to give the dose once each day. Your doctor will work out the dose you need to give.

If you use more NULIBRY than you should
If you think you or your child may have been given more NULIBRY than prescribed, tell your doctor immediately.

If you forgot to give a dose of NULIBRY.
If a dose of NULIBRY is missed, give the missed dose as soon as possible. Wait at least 6 hours before you give the next dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if any of the side effects occur, or if you notice any side effects not listed in this leaflet.

The following side effects are very common and are related to the injection device (catheter) and not to the medicine. These may affect more than 1 in 10 people:
- Catheter-related problems, such as pain, discharge, redness, or inflammation

Complications related to catheter
You or your child will have an injection device (catheter-type device). This is used to inject medicines into you or your child's blood. You or your child may develop complications related to the catheter. Please follow the instructions from your doctor or nurse on how to care for this device before and after giving a dose of NULIBRY.

Reporting of side effects
If you notice any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store NULIBRY

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Unopened vial
Store in a freezer at -25 °C to -10 °C.
Keep the vial in the outer carton in order to protect from light.

Storage of the reconstituted (mixed) NULIBRY
Reconstituted NULIBRY may be stored at room temperature (15 °C-25 °C) or refrigerated (2 °C-8 °C) for up to 4 hours including the time needed to give NULIBRY.

If reconstituted NULIBRY is refrigerated, allow it to come to room temperature (by rolling each vial gently between your hands for 3 to 5 minutes (do not shake) or by leaving it at room temperature for approximately 30 minutes) before giving NULIBRY.
- Do not heat.
- Do not freeze NULIBRY after reconstitution.
- Do not shake.

The reconstituted solution must be a clear and colourless to pale yellow solution. Do not use this medicine if you notice any particles or if the solution is discoloured.

Do not throw away any medicines or waste material, including materials used for reconstitution and administration via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What NULIBRY contains

- The active substance is fosdenopterin 9.5 mg. Each vial contains fosdenopterin hydrobromide dihydrate equivalent to 9.5 mg fosdenopterin.
- The other ingredients are: ascorbic acid (E300), mannitol (E421), sucrose, hydrochloric acid (E507), sodium hydroxide (E524) (see section 2 "NULIBRY contains sodium").

What NULIBRY looks like and contents of the pack
NULIBRY is a white to pale yellow powder for solution for injection (powder for injection).

Each pack contains one vial.

Marketing Authorisation Holder
TMC Pharma (EU) Ltd
G24A Arc Labs Research and Innovation Centre,
SETU West Campus, Carriganore,
Waterford, X91 P20H,
Ireland

Manufacturer
Sciensus International B.V.
Bijsterhuizen 3142
6604 LV Wijchen,
The Netherlands

This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for preparation and administration of NULIBRY:

Instructions for use on how to prepare and give NULIBRY.

Read these instructions for use before you reconstitute (mix) and give a dose of NULIBRY for the first time and each time you get a NULIBRY refill. This information does not replace talking to your doctor about your child's medical condition or their treatment. Always talk to your doctor if you are unsure.

Your doctor should show you the right way to prepare and give your child's prescribed dose of NULIBRY before you do this for the first time.

NULIBRY is given into your child's vein (intravenously), through a catheter-type device which is placed by your doctor or nurse. Always follow the specific instructions given by your doctor or nurse.

Important information you need to know before preparing and giving NULIBRY

- Your child's dose of NULIBRY is based on their age and body weight. Your doctor or nurse will work out the amount of NULIBRY needed for each dose for your child. The amount of NULIBRY needed for each dose and the number of vials needed to prepare each dose may change at each visit with your doctor. The dose will be measured as the number of millilitres (mL) of solution that you need to give.
- If you or your child's caregiver are administering NULIBRY at home, your doctor or nurse will suggest that you keep an infusion diary including at minimum:
  - date of each dose of NULIBRY
  - number of vials used to prepare each dose
  - lot number from each NULIBRY vial used
  - total amount (number of mL) of NULIBRY that was given
  - start and end time of the dose
  - a place to capture adverse events, medication errors, and complications with the administration

  Be sure to keep this information up to date when the dose changes. Bring your infusion diary to each follow-up visit with your doctor. Be sure to have your doctor or pharmacist fill in the following information on your infusion diary:
  - your child's dose of NULIBRY in millilitres (mL)
  - number of vials needed to prepare each dose

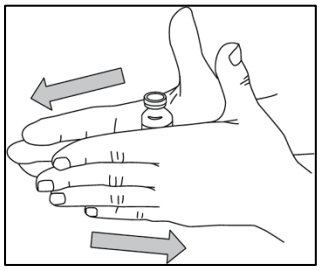
- NULIBRY comes as a powder in a vial. Each vial of NULIBRY must be made up with 5 mL of sterile water for injection to dissolve the powder and make a solution before use.
  Do not prepare the solution with anything other than sterile water for injections.

NULIBRY must be given within 4 hours of preparing the solution. You may keep the prepared solution of NULIBRY at room temperature or refrigerated for up to 4 hours, including the time necessary to give the dose. If you do not give the prepared dose of NULIBRY within 4 hours, all the solution you have made must be thrown away. See section 5 of the package leaflet **"How to store NULIBRY".**

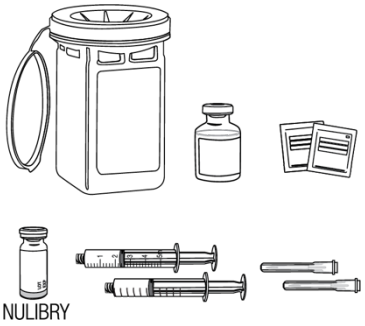
Preparing to give NULIBRY

Step 1: Gather Supplies

- Use a clean, flat work surface.
- Remove from the freezer the correct number of NULIBRY vials needed to prepare your child's prescribed dose. You may need more than 1 vial to prepare the total amount needed for 1 dose. Allow the NULIBRY vials to reach room temperature. This can be done by rolling each vial gently between your hands for 3 to 5 minutes as shown, or by allowing the vials to sit at room temperature for about 30 minutes.



- Gather supplies needed to prepare and give a dose of NULIBRY:
  - 1 vial of sterile water for injection for each vial of NULIBRY needed for 1 dose.
    - Check the expiry date on the NULIBRY vial. Do not use the vial if the expiry date has passed.
    - Do not use the vial if the flip-off seal on the vial is broken or missing.
  - 1 sterile 5 mL syringe for each vial of NULIBRY needed for 1 dose, used to prepare NULIBRY with sterile water for injection
  - A second sterile syringe large enough to hold the total amount of NULIBRY needed for one dose. Your doctor, nurse or pharmacist should tell you what size and type of syringe to use.
  - sterile needles (18-gauge recommended)
  - alcohol wipes
  - gloves, if your doctor or nurse has instructed you to wear gloves when preparing and giving NULIBRY
  - 1 intravenous administration set requires specific tubing [di(2-ethylhexyl)phthalate (DEHP)-free tubing with a 0.2 micron filter]
  - 1 infusion pump used to give the dose of NULIBRY as instructed by your doctor
  - other materials, if recommended by your doctor to properly care for your child's intravenous catheter-type device before and after giving a dose of NULIBRY
  - Any other materials provided by your pharmacist to throw away medicines you no longer use. These measures will help protect the environment.

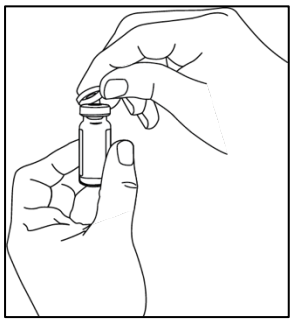


Step 2: Wash your hands

- Wash your hands well with soap and water. Use a clean towel to dry your hands or allow them to air dry.
- If you have been told to wear gloves to prepare and give NULIBRY, put them on now.

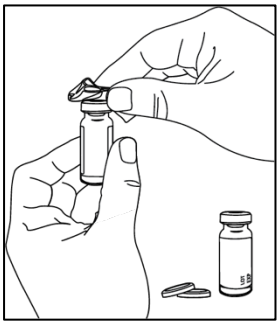
Step 3: Prepare the vials

- Remove the flip-off cap from each vial of sterile water for injection needed.



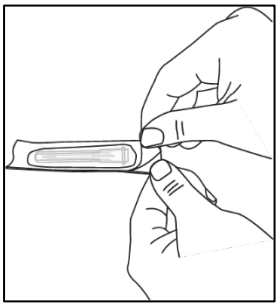
- Clean the rubber stopper of each vial with an alcohol wipe and allow to air dry. Do not blow on the stopper to dry it faster.

Note: If you touch the vial stopper, you will need to clean it again with an alcohol wipe.

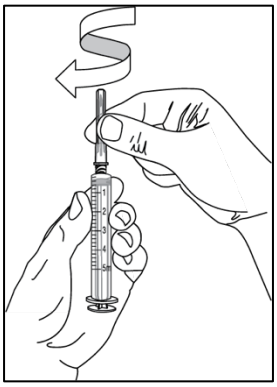


Step 4: Prepare the syringe used for drawing up sterile water for injection

- Open the wrapper that contains a needle. **Do not** remove the needle cover yet.

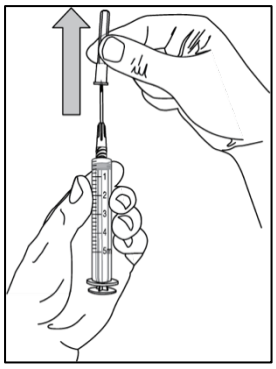


- Open the wrapper that contains a 5 mL syringe. Attach the needle to the syringe tip by screwing it on, turning in the direction of the arrow as shown. Your needle and syringe may look different to those shown.

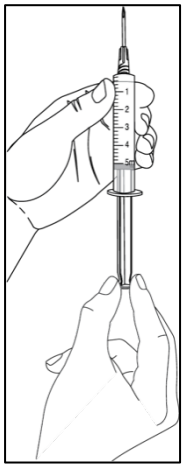


Step 5: Fill syringe with sterile water for injection

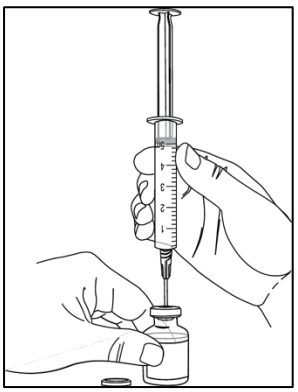
- Remove the needle cover by pulling the cover straight off. **Do not** touch the needle or let the needle touch any surface.



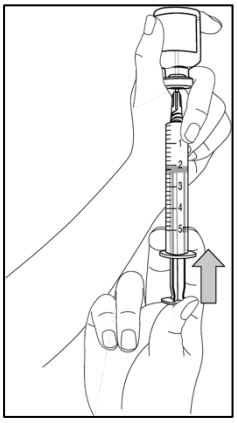
- Hold the body of the syringe with one hand. Use your other hand to pull back the plunger of the syringe until the top of the plunger reaches the 5 mL line on the syringe.



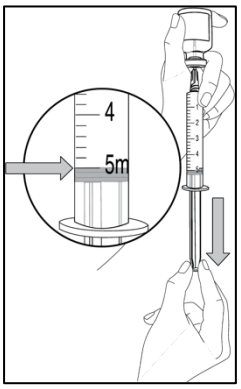
- Hold the vial of sterile water for injection firmly on your work surface and insert the needle into the centre of the vial stopper.



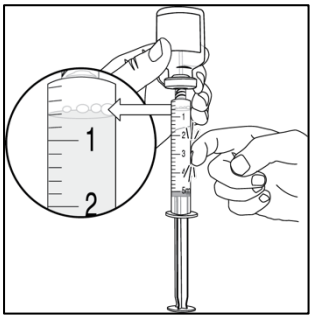
- Slowly turn the vial upside down. Check that the tip of the needle is not in the water. Then, push up on the plunger to push all of the air from the syringe into the vial.

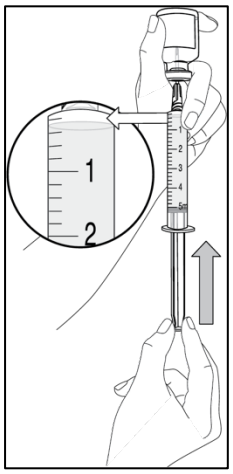


- Next, move the needle so that the tip is in the water. Slowly pull down on the plunger of the syringe to fill the syringe with 5 mL of sterile water for injection.

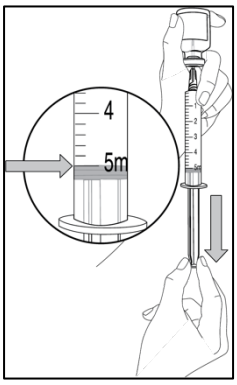


- Tap the syringe with your fingers until any air bubbles rise to the top of the syringe then gently push up on the plunger to push the air out of the syringe.



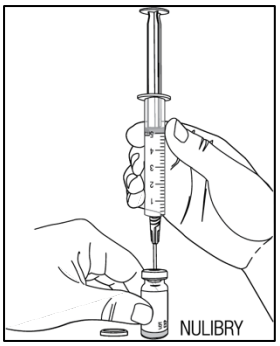


- After removing the air bubbles, check the syringe to be sure that 5 mL of solution is in the syringe before removing the needle from the vial. Continue to draw fluid until you reach 5 mL. Do not use less.



Step 6: Reconstitute NULIBRY

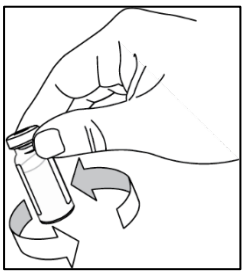
- Remove the flip-off cap from the vial of NULIBRY.
- Wipe the rubber stopper on the vial of NULIBRY with a new alcohol wipe.
- Hold the NULIBRY vial firmly on your work surface. Take the syringe with the sterile water for injection and slowly insert the needle into the centre of the vial stopper.



- Slowly push down on the plunger all the way to push the sterile water for injection into the vial. Then carefully remove the needle from the vial. Throw away the used needle and syringe right away as your pharmacist instructed you, so that

nobody can be injured. **Do not** try to recap the needle. See section 5 "**How to store NULIBRY**"

- Gently swirl the vial continuously until the powder is completely dissolved. **Do not** shake the vial.

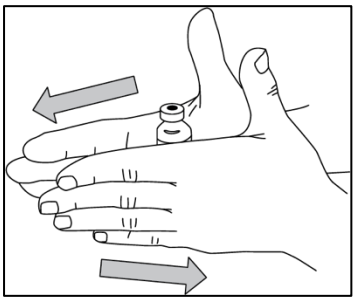


- **Repeat steps 4 through 6 if more than 1 vial of NULIBRY is needed to prepare your child's prescribed NULIBRY dose.**
- **Use a new 5 mL syringe and new needle for each vial of NULIBRY.**

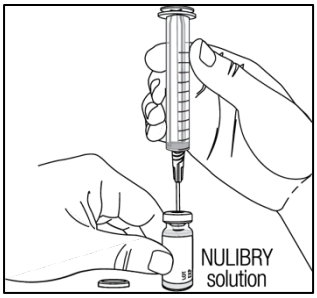
Note: Once prepared, the NULIBRY solution should be clear, and colourless to pale yellow.

- **Do not** use the solution if it is discoloured or cloudy, or if there are any particles in it. If the solution is discoloured or cloudy or there are particles in it:
  - **Do not** throw the vial away because the pharmacist may ask that you return it.
  - Tell your pharmacist and ask for a replacement vial.

Step 7: Prepare a syringe with the prescribed dose of NULIBRY

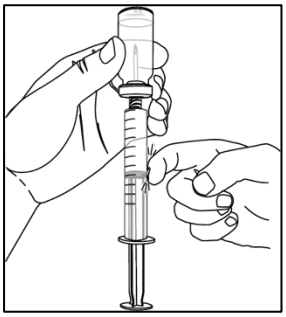


- If you stored the prepared NULIBRY solution in the refrigerator, remove the vials of prepared NULIBRY solution from the refrigerator and allow them to reach room temperature. This can be done by rolling each vial gently between your hands for 3 to 5 minutes as shown (do not shake), or by allowing the vials to sit at room temperature for about 30 minutes.
- Open the wrapper that contains a new sterile needle. **Do not** remove the needle cover yet.
- Open the wrapper that contains a sterile disposable syringe that is large enough to hold the total volume of NULIBRY needed for one dose. Attach the needle to the syringe tip with a screw action. **Do not** remove the needle cover yet.
- Wipe the vial stopper of each prepared NULIBRY vial with a new alcohol wipe.
- Remove the needle cover by pulling the cover straight off. **Do not** touch the needle or let the needle touch any surface.
- Hold the syringe with one hand. Insert the needle into the centre of the NULIBRY vial stopper then slowly turn the vial upside down.



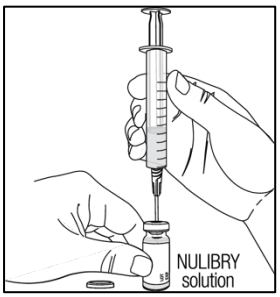
- Next, move the needle so that the tip is in the NULIBRY solution. Slowly pull back on the syringe plunger to fill the syringe with the amount of NULIBRY solution in mL for your child's prescribed dose.

- Remove any air bubbles from the syringe. Tap on the syringe barrel so that any bubbles rise to the top of the vial. Push up on the plunger to push any air bubbles back into the vial. Check to make sure that the correct amount of NULIBRY solution has been drawn into the syringe. If needed, pull down slightly on the plunger until the prescribed amount of NULIBRY solution is in the syringe.

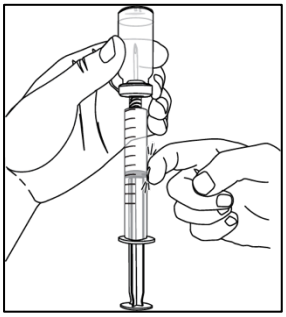


Follow the steps below if more than 1 vial of NULIBRY is needed to make up the total amount of solution needed for 1 daily dose.

- Remove the needle and syringe from the first vial of NULIBRY. Hold the syringe with one hand. Insert the needle into the centre of the next NULIBRY vial stopper then slowly turn the vial upside down.

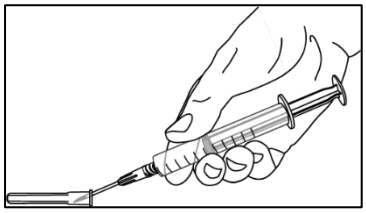


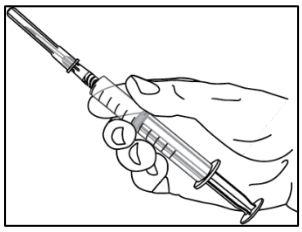
- Next, move the needle so that the tip is in the NULIBRY solution. Slowly pull back on the syringe plunger to fill the syringe with the amount of NULIBRY solution in mL for your child's prescribed dose.
- Remove any air bubbles from the syringe. Tap on the syringe barrel so that any bubbles rise to the top of the vial. Push up on the plunger to push any air bubbles back into the vial. Then check to be sure that the prescribed amount of NULIBRY solution has been drawn into the syringe. If needed, pull down slightly on the plunger until the total prescribed amount of NULIBRY solution is in the syringe.

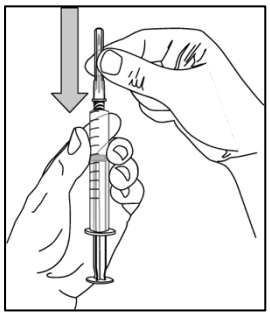


- Repeat this step if additional vials of NULIBRY are needed to make up your child's dose.
- When the needle is removed from the last vial of NULIBRY, all of the prepared dose of NULIBRY is in 1 syringe.

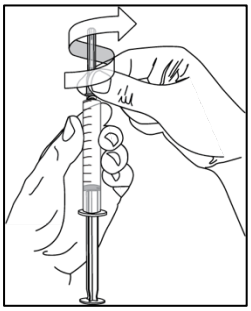
- Replace the needle cover before removing the needle from the syringe by placing the cover on a flat surface and sliding the needle into the cover as shown. With one hand, hold the syringe and use the needle to "scoop up" the cover. Once the cover is on the needle, use the other hand to secure the cover on the needle hub.







- Remove the covered needle from the syringe tip with a screw action in the direction of the arrow as shown.
  Do not touch the tip of the syringe after removing the needle.



- Throw away the needle properly. See section 5 **"How to store NULIBRY"**

- Throw away the used NULIBRY vial(s) after use, even if there is medicine left in the vial as instructed by your pharmacist. Do not throw it out with the household waste.
- The dose of NULIBRY is now ready to be given to your child.

Step 8: Giving a dose of NULIBRY

- NULIBRY is given into your child's vein (intravenously) through a catheter-type device placed by your doctor.
- When NULIBRY is given through an infusion pump, infuse NULIBRY at a rate of 1.5 mL per minute.

- If the amount (volume) in mL for your child's prescribed dose of NULIBRY is less than 2 mL, your doctor may tell you to give NULIBRY by injecting it slowly using a syringe. Follow your doctor's instructions for how to give your child's dose of NULIBRY by slow injection.
- **Follow your doctor's instructions for proper care of your child's intravenous access catheter-type device before and after giving a dose of NULIBRY.**

Step 9: Record the injection
After giving each dose of NULIBRY, record information about the dose in an infusion diary. See the section of this instructions for use called "**Important information you need to know before preparing and giving NULIBRY.**"

Step 10: Disposal
After injection, safely throw away all unused NULIBRY solution, the syringe with the injection set, the vial and other waste materials as instructed by your pharmacist.
Do not throw it out with the household waste. These measures will help protect the environment.