Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for patients

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines (medicines that do not have a marketing authorisation or are used outside their licence) to UK patients that have a high unmet clinical need. The medicines included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here:
http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

The information below is intended for you, the patient, and is provided by the pharmaceutical company (called scientific opinion holder) that manufactures the EAMS medicine. This medicine, which does not yet have a drug licence or is used outside its licence, may also be used in combination with other medicines. More information about medicines licensing can be found here:
http://www.nhs.uk/conditions/medicines-information

This medicine can be prescribed for individual patients to meet specific needs provided they are given sufficient information about the medicine to make an informed decision. The prescribing doctor will be responsible for giving you all the information you need to make this decision and for obtaining informed consent from you prior to treatment. You will be asked to sign a form to confirm that you are providing informed consent to receiving the EAMS treatment. Information on consent can be found here: https://www.nhs.uk/conditions/Consent-to-treatment

The information below is provided to help you decide with the prescribing doctor on whether to use the EAMS medicine and helps explain how to use it in accordance with the pharmaceutical company's instructions for safe and proper use. The information below may change during the time you are using the medicine if more data become available. The prescribing doctor will highlight to you any changes that you need to be aware of.

Whilst you are using this medicine, data will be collected on the use and safety profile of the medicine, to ensure that the benefits of taking the medicine continue to outweigh any potential risks. The prescribing doctor will answer all your questions during and after the treatment and will provide you with contact details that you should use in case of any events or problems.

Each patient enrolled in the scheme will continue to receive the EAMS product until the end of the treatment in line with prescribing and NHS guidance and as long as benefit is seen. In rare cases where the EAMS treatment may not be available anymore, your prescribing doctor will discuss other options with you.

Information for the Patient

Doxecitine and Doxribtimine 4 g powder for oral solution (2 g each)

Doxecitine and Doxribtimine

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See Section 4.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- The full name of your medicine is doxecitine and doxribtimine 4 g powder for oral solution (2 g each). In this leaflet, the shorter name 'doxecitine and doxribtimine' is used.
- It is important that you keep the EAMS Patient Alert Card with you at all times during treatment (the EAMS Patient Alert Card will fit in a wallet) and at least for a month after completing treatment with doxecitine and doxribtimine.
- Always tell any doctor or other healthcare professional treating you that you are taking doxecitine and doxribtimine and show them your EAMS Patient Alert Card (this includes your GP, dentist, nurse, or pharmacist).

What is in this leaflet

- **WHAT DOXECITINE AND DOXRIBTIMINE IS AND WHAT IT IS USED FOR**

What doxecitine and doxribtimine is

Doxecitine and doxribtimine is known as nucleoside therapy. Doxecitine and doxribtimine contains a 1:1 mixture of the active substances doxecitine and doxribtimine, which are nucleosides and are used by the body to build deoxyribonucleic acid (DNA), among other functions.

What doxecitine and doxribtimine is used for

Doxecitine and doxribtimine is an experimental drug for investigational use to treat thymidine kinase 2 deficiency (TK2d), a rare form of inherited mitochondrial DNA depletion and deletion syndrome, in children and adults with an age of symptom onset at or before 12 years. Mitochondria are part of the cell that produce the cell's energy and they carry their own genetic

material, mitochondrial DNA. The disease affects mainly the muscles and causes muscle weakness, including in the limbs and in muscles required for breathing and feeding.

How doxecitine and doxribtimine works

Doxecitine and doxribtimine work by restoring the mitochondrial DNA levels that are depleted in TK2d.

- **WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN DOXECITINE AND DOXRIBTIMINE**

Do not take doxecitine and doxribtimine if:

Do not take doxecitine and doxribtimine if you are allergic to doxecitine, doxribtimine or any of the other ingredients of this medicine listed in Section 6 Contents of the pack and other information.

Warnings and precautions

Before you get doxecitine and doxribtimine, tell your doctor if you:

- you have or have had liver problems because increase in liver function tests can occur during treatment with doxecitine and doxribtimine. Your doctor will check your liver both before and during treatment.
- You have diarrhoea, as your doctor may need to adjust your dose.

Other medicines and doxecitine and doxribtimine

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

In particular, tell your doctor if you are taking any of the following medicines:

- medicines able to kill cells, such as cancer cells, and antiviral medicines (e.g., cedazuridine, cisplatin, tipiracil, brivudine, stavudine, ribavarin, fludarabine)

The use of any other investigational agents for treatment of TK2d is not permitted while the patient is participating in the Treatment Protocol. This includes the use of non-GMP doxecitine and doxribtimine or dNMPs, which are prohibited while enrolled in the Treatment Protocol.

Doxecitine and doxribtimine with food, drink and alcohol

- This medicine must only be mixed with water.
- Do not directly prepare the powder with food or other liquids.

Pregnancy and doxecitine and doxribtimine

This section outlines the pregnancy-related risks associated with using doxecitine and doxribtimine.

- If you are a female who can become pregnant, you:
  - will need a pregnancy test before starting treatment,
  - must use effective birth control, and
  - must report any pregnancies promptly.
- If you are a sexually active male, you must ensure effective contraception for your partners to avoid potential risks to a fetus.
- If you become pregnant during the treatment period, prompt communication with your physician is crucial.
- There are concerns about unknown fetal risks and long-term effects.

- Breastfeeding is not recommended during treatment.

Driving and using machines

This medicine has no, or almost no effect on your driving and use of machines.

For more information:

Refer to your informed consent form (ICF) or other information provided to you by your doctor.

- **HOW TO TAKE DOXECITINE AND DOXRIBTIMINE**

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

Treatment must be started and supervised by a doctor experienced in the treatment of the disease.

Dosing doxecitine and doxribtimine

- The dose of the doxecitine and doxribtimine oral solution is based on your weight. Your doctor will tell you the number of sachets and volume of water you have to use for the preparation of your daily supply.
- The daily recommended starting dose is 130 mg of doxecitine and 130 mg of doxribtimine for each kg of body weight per day.
- Your doctor may change your dose based on tolerability.
- Your doctor may change the number of sachets to achieve the recommended dose based on changes in your weight.
- Always take this medicine with food.

Preparing doxecitine and doxribtimine

- The doxecitine and doxribtimine oral solution must be prepared as a single daily dose each day. This daily dose is then measured and administered orally in three equally divided individual doses throughout the day (see Taking doxecitine and doxribtimine
- below).
- Doxecitine and doxribtimine must only be prepared with room temperature water.
- Do not mix doxecitine and doxribtimine powder with other medicines, liquids, powders, or foods.
- You must carefully read and follow the enclosed "Instructions for Use (IFU)" on how to prepare and take doxecitine and doxribtimine.

Taking doxecitine and doxribtimine

- The doxecitine and doxribtimine oral solution must be taken by mouth (orally) 3 times a day in equally divided doses, approximately 6 hours apart ±2 hours, with food.
- If a dose is spit up or if you are not sure that all of the medicine was taken, do not take another dose. Wait until the next scheduled dose.
- After preparation, the solution should be used within 16 hours because the solution is stable only during that period.
- The prepared solution can be stored at room temperature, not above 25°C (or 77°F), or in the refrigerator between 2°C to 8°C (or 36°F to 46°F).

- If necessary, this medicine may be administered via an enteral feeding tube with or after a feed.

Using an enteral feeding tube

- The doxecitine and doxribtimine oral solution is compatible with most enteral feeding tubes (polyurethane, polyvinyl chloride, silicone) from 4 French and up with a maximum length of 125 cm.
- Do not mix doxecitine and doxribtimine powder with other medications, liquids, powders or foods.
- Be sure doxecitine and doxribtimine is administered with or after a feed.
- If you take or give doxecitine and doxribtimine via an enteral feeding tube, (nasogastric tube, gastrostomy tube), ensure you follow manufacturer's instructions. For more information, ask your doctor, pharmacist or nurse.

If you take more doxecitine and doxribtimine than you should

If you suspect that you have accidentally taken a higher dose of doxecitine and doxribtimine than prescribed, please contact your doctor for advice as soon as possible.

If you forget to take doxecitine and doxribtimine

If you miss a dose, you should take the dose as soon as you remember. However, if it is less than 2 hours to the next dose, the dose should not be taken. You should take the next dose at the usual time. A double or extra dose should not be taken to make up for the missed dose.

If you stop taking doxecitine and doxribtimine

Interrupting or stopping treatment with this medicine may cause your symptoms to come back. Talk to your doctor before stopping doxecitine and doxribtimine. Your doctor will discuss the possible side effects and risks with you. Your doctor may also want to monitor you closely.

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

- **POSSIBLE SIDE EFFECTS**

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

Very common side effects (may affect more than 1 in 10 people)

- diarrhoea
- vomiting
- abdominal pain
- upper abdominal pain

Reporting of side effects

If you get any side effects, please report them to your doctor, pharmacist or nurse.

- **HOW TO STORE DOXECITINE AND DOXRIBTIMINE**
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which can sometimes be found on the carton ("EXP"). The expiry date refers to the last day of that month.

- Doxecitine and doxribtimine packets and cartons should only be kept at room temperature.

Reconstituted solution

- After reconstitution, the solution should be used within 16 hours.
- Reconstituted solution can be stored at room temperature (up to 25° C or 77° F) or in a refrigerator (2°C-8°C or 36°-46°F).
- Do not freeze.
- Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

- **CONTENTS OF THE PACK AND OTHER INFORMATION**

What doxecitine and doxribtimine contains

- The active substances are doxecitine and doxribtimine. One sachet contains 4 g of doxecitine and doxribtimine powder for oral solution (2 g of doxecitine and 2 g doxribtimine).
- The other inactive ingredients are silica colloidal anhydrous and magnesium stearate.

What doxecitine and doxribtimine looks like and contents of the package

Doxecitine and doxribtimine is a white to off-white powder for oral solution, supplied in a sachet.

Instructions for Use

Table of contents

- Contact your healthcare provider or pharmacist

Instructions For Use

Important information

These Instructions for Use contains information on how to prepare and take "or give" a one-day supply of KYGEVVI.

Read these Instructions for Use before taking or giving KYGEVVI and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

When you are prescribed KYGEVVI for the first time, you will be provided with the carton(s) of 30 KYGEVVI powder sachets and the Administration device kit (see **Figure A**).

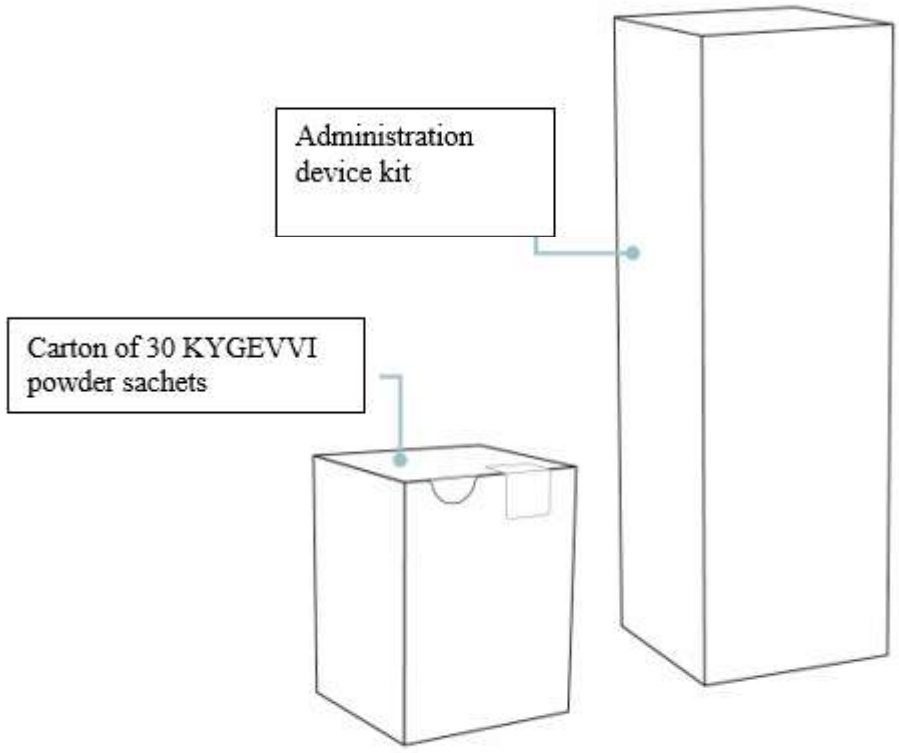
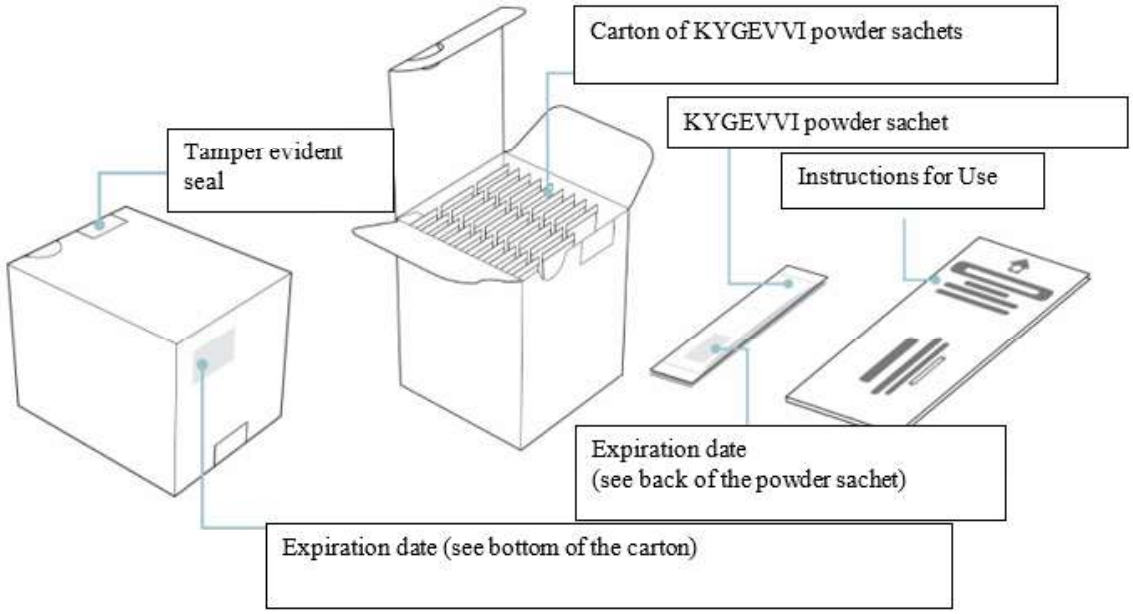


Figure A

Before you start

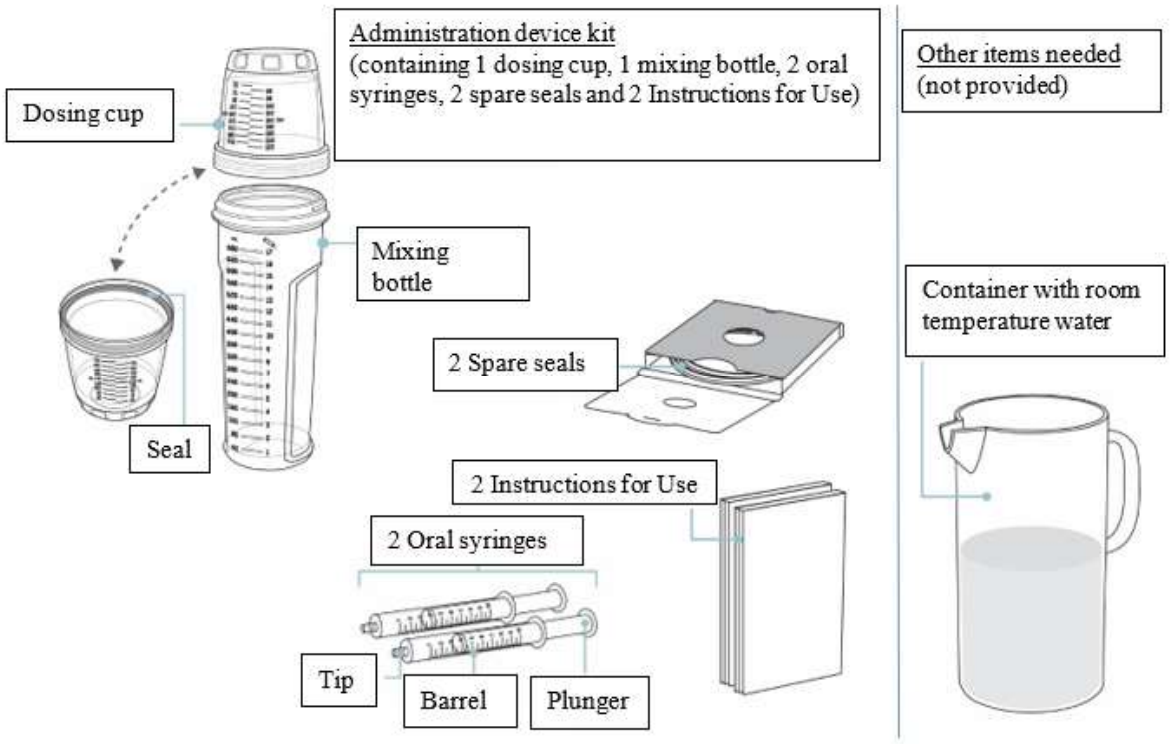
Supplies for preparing and taking or giving KYGEVVI

Carton of 30 KYGEVVI powder sachets



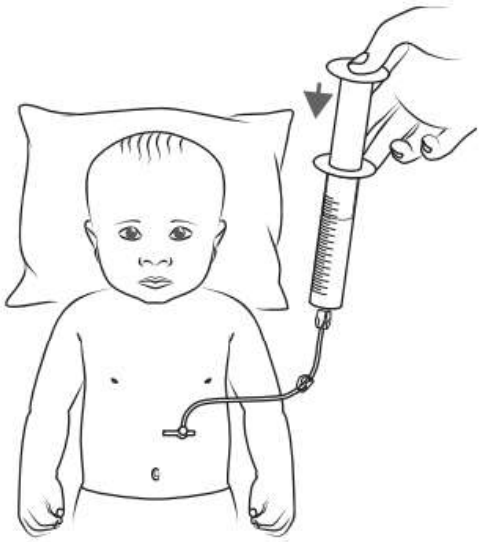
Before you start

Supplies for preparing and taking or giving KYGEVVI



- You will prepare a **one-day supply** of KYGEVVI oral solution to be taken in **3 equal doses** throughout the day (about **6 hours** apart).
- If you or the patient you care for weigh more than 85.0 kg, your doctor may tell you that you need to prepare your 3 daily doses separately. It is important to talk to your doctor about the detailed preparation steps if this is the case.
- KYGEVVI should be prepared and given by adults only.
- Only use the dosing cup, mixing bottle and oral syringes provided with your Administration device kit.
- Each Administration device kit includes two oral syringes. Keep the second oral syringe as a spare.
- Rinse and dry the mixing bottle and dosing cup before first use. **Do not** use the dosing cup, mixing bottle or oral syringe if it appears dirty or damaged.
- Each Administration device kit can be used for 6 months. Contact your healthcare provider when you need a replacement.
- Contact your healthcare provider or pharmacist for a replacement if your mixing bottle, dosing cup, or oral syringe is damaged or if the markings are missing or no longer readable.
- **Do not** use the powder sachets if the tamper evidence seal on the carton is broken.
- Mix KYGEVVI powder only with room temperature water. **Do not** mix KYGEVVI powder with cold or hot water, milk powders or any other liquids or foods. You may have KYGEVVI oral solution left over after taking your 3 individual doses. Throw away (dispose of) any remaining KYGEVVI oral solution at the end of each day.
- If powder spills out of a sachet before use, **do not** use the sachet. Throw it away and use a new KYGEVVI powder sachet.

KYGEVVI oral solution is compatible with most feeding tubes. Follow the steps in this instruction booklet to prepare your one-day supply of KYGEVVI and then follow the feeding tube instructions to give KYGEVVI using a feeding tube.



Preparing your one-day supply of KYGEVVI

Get supplies ready

Step 1

a) Wash your hands well with soap and water.
b) Place the mixing bottle, dosing cup and the oral syringe (if you need one to measure your individual dose) on a clean, well-lit flat work surface. If the dosing cup is attached to the mixing bottle, unscrew it from the mixing bottle and set it down (see **Figure B**).
c) When opening the KYGEVVI carton for the first time, break the tamper evidence seal.
d) Remove the prescribed number of KYGEVVI powder sachets needed for your one-day supply of KYGEVVI out of the carton. Your one-day supply of KYGEVVI will be divided into 3 individual doses.
e) **Do not** open the KYGEVVI powder sachets until Step 2.

Note: The mixing bottle has markings on the front of the bottle in 40 ml increments, each increment is equal to one sachet of medicine.

The dosing cup has markings on the front and back of the cup in 10 ml increments, offset to provide 5 ml increments of measurements.

Figure B

Preparing your one-day supply of KYGEVVI

Measure water and add powder sachets

Step 2

a) On a flat surface, pour the prescribed amount of room temperature water into the mixing bottle (see **Figure C**).
   - **Do not** pour the water into the dosing cup.
   - **Important: Do not** add powder sachets to the mixing bottle before this step.

b) Check to make sure the mixing bottle is filled with water up to the marking that matches the amount prescribed by your healthcare provider. The marking should also match the number of sachets needed for your one-day supply (see **Figure C)**.
c) Check you have counted out the correct number of KYGEVVI powder sachets for your one-day supply, as shown on your prescription.
d) Tap the powder sachet on a hard surface to settle the powder to the bottom of the sachet away from the dotted line (see **Figure D**).
e) Carefully fold and tear or cut along the dotted line (see **Figure E**). If you spill any powder, **do not** use it. Throw the powder sachet away and use a new sachet.
f) Empty the entire powder sachet contents into the mixing bottle containing water. Be careful not to drop the powder sachet into the mixing bottle (see **Figure F**).
g) Pour only 1 powder sachet into the mixing bottle at a time. Repeat **Steps 2d** to **2f**, for each powder sachet until you have poured the prescribed number of powder sachets for your one-day supply.

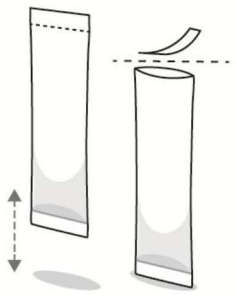


Figure C **Figure D** **Figure E** **Figure F**

Preparing your one-day supply of KYGEVVI

Mix and inspect medicine

Step 3

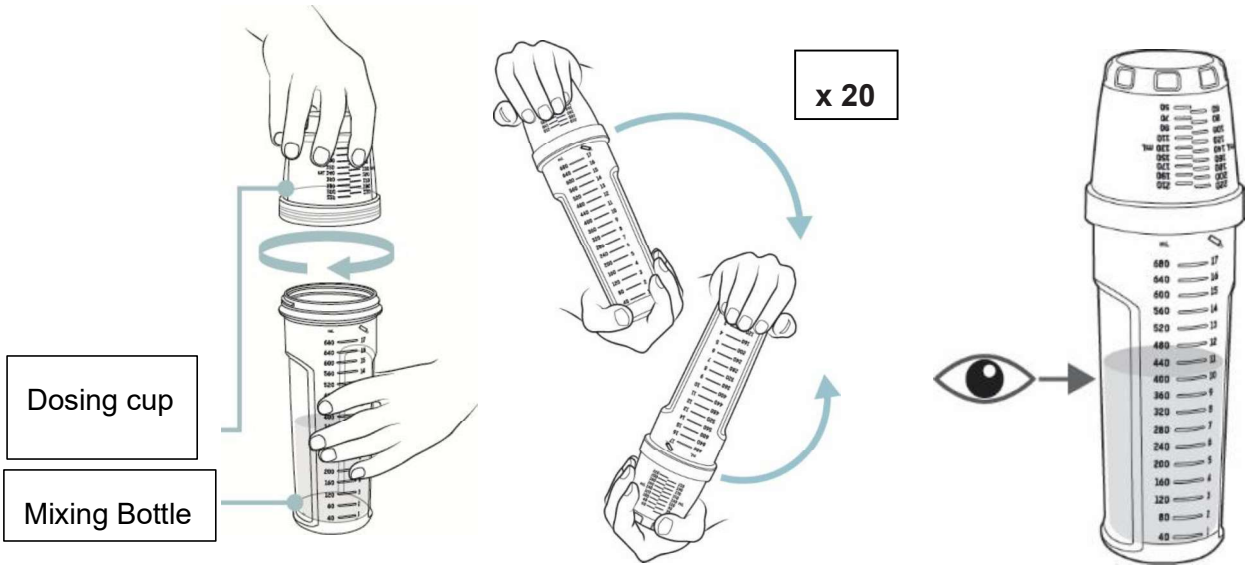
a) Screw the dosing cup tightly onto the mixing bottle (see **Figure G**).
b) Place one hand at the end of the mixing bottle and the other hand at the end of the dosing cup. Slowly turn the bottle upside down and back. **Repeat at least 20 times**

(see **Figure H**).

c) Check the solution. If you see any lumps, keep turning until they disappear (see **Figure I**).
d) The solution will be cloudy and have some powder residue at the bottom or top, this is normal.

You have now prepared your one-day supply of KYGEVVI oral solution for **3 individual doses** or your individual dose if your doctor has told you to prepare your individual doses separately. Take KYGEVVI oral solution with a snack or meal.

Figure G **Figure H** **Figure I**



Dosing methods

How to measure your individual dose

There are 2 different methods to take or give KYGEVVI oral solution depending on your individual dose. Use the table below to identify which steps you should follow:

Doses **equal to** or **greater** than 50 ml	Doses **less** than 50 ml (dosing cup used for dose preparation only)
Example 100 ml  Follow **Step 4**	**Example 14 ml**  Follow **step 5**

Individual doses equal to or greater than 50 ml

Measure and take or give your individual dose

You will need to use the dosing cup to measure and take or give your individual dose.

Step 4. Individual doses equal to or greater than 50 ml

a) Check to ensure the dosing cup is closed tightly onto the mixing bottle and mix the already prepared oral solution by slowly turning the mixing bottle upside down and back at least 3 times.
b) Unscrew the dosing cup from the mixing bottle and place on a flat surface.
c) Pour KYGEVVI oral solution from the mixing bottle into the dosing cup until it reaches the marking on the dosing cup for your prescribed individual dose (see **Figure J**). **Note:** Your dose may be different than the dose shown in Figure J.
d) Drink or give the entire oral solution from the dosing cup (see **Figure K**).

e) When it is time for the **second or third individual dose**, repeat **Steps 4a** to **4d** for each individual dose.
f) After the **first or second individual dose**, go to **Step 6** for instructions on how to clean your supplies and store KYGEVVI oral solution. After the **third individual dose**, go to **Step 7** for instructions on how to clean your supplies and dispose of KYGEVVI oral solution.

Figure J

Figure K

Individual doses less than 50 ml

Measure and take or give your individual dose

Step 5 – Individual doses less than 50 ml

You will need to use the dosing cup and oral syringe to measure and take or give your individual dose

a) Mix the already prepared oral solution by slowly turning the mixing bottle upside down and back at least 3 times.
b) Unscrew the dosing cup from the mixing bottle and place on a flat surface.
c) Pour slightly more than the amount of oral solution needed for your prescribed individual dose into the dosing cup (see **Figure L**).
d) Push the plunger of the oral syringe all the way down to make sure there is no air in the oral syringe when measuring the dose (see **Figure M**).

If you are giving the oral solution to young children, they must be seated and held in place to avoid the risk of oral solution going down the wrong pipe or choking.

e) Place the tip of the oral syringe into the dosing cup with the oral solution. Fill the oral syringe by pulling the plunger back until it reaches the marking on the oral syringe that matches your prescribed individual dose (see **Figure N**). **Step 5e** may need to be repeated depending on your individual dose.

Figure L

Figure N

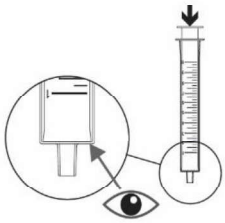


Figure M

f) Place the tip of the oral syringe into the mouth and point the tip towards the inside of either cheek (see **Figure O**).
g) Slowly push the plunger all the way down until the oral syringe is empty (see **Figure O**).

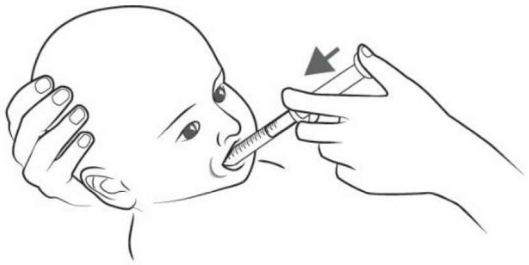


Figure O

h) If your prescribed dose is more than 10 ml, repeat **Steps 5d** to **5g** until you take or give the full individual dose.
i) Pour back any remaining oral solution from the dosing cup into the mixing bottle.
j) When it is time for the **second or third individual dose**, repeat **Steps 5a** to **5i** for each individual dose.
k) After the **first or second individual dose**, go to **Step 6** for instructions on how to clean your supplies and store KYGEVVI. After the **third individual dose**, go to **Step 7** for instructions on how to clean your supplies and dispose of KYGEVVI.

Between individual doses

Clean up after first and second individual dose

Step 6.

After you complete the first or second individual dose:

- Rinse the dosing cup with cold water after each use (see **Figure P**).
- Dry the dosing cup with a clean, dry towel.
- After the dosing cup is dry, screw the dosing cup tightly onto the mixing bottle (see **Figure Q**) and store it at room temperature or in the refrigerator until it is time for the next individual dose.
    - If you used the oral syringe, clean it with cold water:
        - Rinse the oral syringe with cold water by filling the oral syringe with water and pushing it back out (see **Figure R)**. Then remove the plunger from the barrel and rinse the plunger and barrel (see **Figure R)** under running tap water until it is clean.
        - Let the oral syringe barrel and plunger dry in the open air. After the oral syringe barrel and plunger are dry, put the plunger back into the barrel.
    - **Do not** wash the dosing cup or oral syringe in the dishwasher.

Figure P

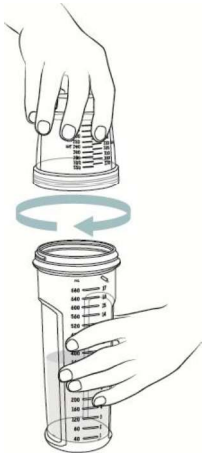


Figure Q

Figure R

End-of-day clean up

Pour out and clean up after third individual dose

Step 7

After you take or give the third individual dose, throw away any remaining KYGEVVI oral solution in the sink.

Do not save KYGEVVI oral solution for another day.

- Remove the seal from the dosing cup to thoroughly clean it (see **Figure S**).
- Clean the mixing bottle, dosing cup and seal by hand with soap and warm water. Use a brush to remove any residue left in the mixing bottle or dosing cup (see **Figure T**).

- Dry the mixing bottle, dosing cup and seal with a clean towel. Put the dry seal back into the dosing cup, with the **thin side of the seal** facing the groove.
- If you used the oral syringe, clean it with cold water:
    - Rinse the oral syringe with cold water by filling the oral syringe with water and pushing it back out (see **Figure U**). Then remove the plunger from the barrel and rinse the plunger and barrel under running tap water until it is clean (see **Figure U)**.
    - Let the oral syringe barrel and plunger dry in the open air. After the oral syringe barrel and plunger are dry, put the plunger back into the barrel.
- **Do not** wash the mixing bottle, dosing cup, seal or oral syringe in the dishwasher.
- Store all supplies in a clean, dry area out of the reach of children for the next day's use.

Figure S

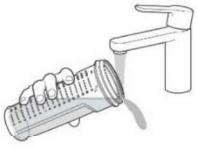


Figure T

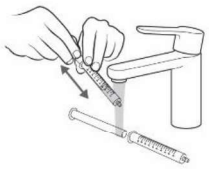


Figure U

Dosing cup maintenance

Replacing the seal if misplaced or damaged

Changing the dosing cup seal

If you misplace the dosing cup seal or you notice leakage when the mixing bottle and dosing cup are tightly closed, change the seal using one of the two spare seals provided in the Administration device kit. Follow these steps to replace the seal:

- Remove the seal in the dosing cup (see **Figure V**). Skip this step if you misplaced the seal.
- Wash the dosing cup groove with warm water (see **Figure W**).
- Get a new seal from the spare seal box (see **Figure X**).
- Insert the seal into the groove of the dosing cup with the **thin side of the seal** facing the groove (see **Figure Y**).

Figure V

Figure W

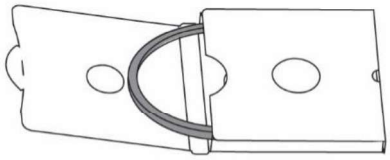


Figure X

Figure Y

Contact your healthcare provider or pharmacist if you have any questions about these Instructions for Use.

DOXECITINE AND DOXRIBTIMINE DOSING QUICK REFERENCE CARD

to be completed by your doctor or authorized health care practitioner

This card provides at-a-glance dosing information about your doxecitine and doxribtimine treatment. Keep it nearby and refer to it as needed.

Patient Name:

Date:

Physician Name:

Physician/Hospital Contact Number:

PREPARE ONE DAILY DOSE

Based on your weight of _____ kg, your doctor has determined you should mix the oral solution as prescribed below to prepare your daily dose.

	IN		PREPARES	
NUMBER of SACHETS		mL of ROOM TEMPERATURE WATER		mL of SOLUTION

ADMINISTER THREE INDIVIDUAL DOSES

_____ml	_____ml	_____ml
morning	afternoon	evening/night

Take your prescribed individual dose of doxecitine and doxribtimine 3 times a day in equally divided doses, approximately 6 hours apart ±2 hours,

You should take doxecitine and doxribtimine with food.

Scientific Opinion Holder

UCB Pharma Ltd
208 Bath Road
Slough, Berkshire
SL1 3WE

Manufacturer

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 1 and 2
73614
Schorndorf
Baden-Württemberg
Germany

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ADDITIONAL INFORMATION:

Informed Consent Form

All patients will have the Early Access to Medicines Scheme explained to them using the informed consent form. The patient will be asked to sign an informed consent form and a copy will be given to them to keep.

CONTACT INFORMATION

Address

UCB Pharma Ltd
208 Bath Road
Slough, Berkshire
SL1 3WE

Email

UCBCares.UK@ucb.com

Telephone

+44 1753 777 100

Reporting of side effects

If you get any side effects, please report them to your doctor, pharmacist or nurse.

Adverse events reporting

Patients must contact their treating physician to report any adverse events. Adverse events may also be reported directly to the MHRA via the Yellow card scheme at:
www.mhra.gov.uk/yellowcard