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

KYGEVVI 2 g/2 g powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet contains 2 g of doxecitine and 2 g of doxribtimine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral solution.
White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KYGEVVI is indicated for the treatment of paediatric and adult patients with genetically confirmed thymidine kinase 2 deficiency (TK2d) with an age of symptom onset on or before 12 years.

4.2 Posology and method of administration

KYGEVVI is intended for use with the instructions and supervision of specialist healthcare professionals experienced in the management of patients with mitochondrial disorders.

Posology

Dosing for KYGEVVI is based on weight of the patient; reassessment of weight should be performed by the prescribing physician.
KYGEVVI is titrated and dosed based on individual patient tolerability, up to a maximum recommended maintenance dose of 400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine.

KYGEVVI should be administered every day in 3 equal doses with food.

Table 1: KYGEVVI recommended dosing schedule[1]:

Initial dosage	130 mg/kg/day of doxecitine and 130 mg/kg/day of doxribtimine
Day 14 Intermediate Dosage	260 mg/kg/day of doxecitine and 260 mg/kg/day of doxribtimine
Day 28 Maintenance Dosage	400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine

[1]For patients with moderate or severe renal impairment a slower titration (at least 4 weeks between each dose increase) should be used.

Tables 2, 3, 4 and 5 show the appropriate number of KYGEVVI powder sachets and required dilution volume by body weight for the recommended dosage levels.

Delayed or missed dose
If a dose is missed, the dose should be taken as soon as possible. However, if it is within 2 hours to the next dose, the dose should not be taken. The patient 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 a dose is spit out or if it is uncertain that all of the medicine was taken, another dose should not be taken. Wait until the next scheduled dose.

Special populations

Elderly
Specific pharmacokinetic evaluations in the elderly have not been performed. No dosage adjustment is recommended in elderly patients based on limited data in patients aged 65 years and older.

Renal impairment
There is no experience with the use of doxecitine and doxribtimine in patients with TK2d with renal impairment. No dosage adjustment is recommended in patients with mild (estimated glomerular filtration rate [eGFR] ≥60 and ≤90 ml/min/1.73 m^2) renal impairment. Specific dosage recommendations cannot be made in patients with moderate (eGFR ≥30 and ≤59 ml/min/1.73 m^2) or severe (eGFR ≥15 and ≤29 ml/min/1.73 m^2) renal impairment (see section 5.2).
Due to the potential for high exposure in patients with moderate or severe renal impairment (see section 5.2) a slower titration (at least 4 weeks between each dose increase) should be used to allow for an assessment of the dose tolerability and to mitigate potential safety consequences of this high exposure to KYGEVVI.

Hepatic impairment
There is limited experience with the use of doxecitine and doxribtimine in patients with hepatic impairment. No dosage adjustment is required in patients with mild hepatic impairment (National Cancer Institute - Organ Dysfunction Working Group (NCI-ODWG) criteria) (see section 4.4). Insufficient data are available to provide a dose adjustment recommendation in patients with moderate or severe hepatic impairment.

Method of administration

KYGEVVI is for oral use.

The reconstituted oral solution should be taken with food 3 times a day in equally divided doses, approximately 6 hours ± 2 hours apart.

Table 2: Recommended initial dosage 130 mg/kg/day of doxecitine and 130 mg/kg/day of doxribtimine oral solution preparation and dosing based on body weight

Body weight (kg)	**Daily oral solution preparation**		**Individual dose volume (ml) (administered 3 times per day)**
	Number of sachet(s) for reconstitution[b]	**Water volume (ml)[a]**	
3.0 – 3.4	1	40	2.5
3.5 - 3.9			3
4.0 - 4.4			3.5
4.5 - 4.9			4
5.0 - 5.9			4.5
6.0 - 6.9			5.5
7.0 - 7.9			6
8.0 - 8.9			7
9.0 - 10.4			8
10.5 - 11.9			10
12.0 - 13.9			11

14.0 - 15.9			13
16.0 - 17.4	2	80	14
17.5 - 18.9			16
19.0 - 20.9			17
21.0 - 24.9			20
25.0 - 27.9			22
28.0 - 31.9			25
32.0 - 34.9	3	120	28
35.0 - 37.9			30
38.0 - 41.9			35
42.0 - 47.9			40
48.0 - 54.9	4	160	45
55.0 - 61.9			50
62.0 - 72.9			55[c]
73.0 - 84.9	5	200	65
85.0 – 92.9	6	240	75
93.0 – 109.9	7	280	85
110.0 – 120.0	8	320	100

[a]Volume of water to reconstitute the powder for the preparation of one day's supply of reconstituted oral solution.
[b]The number indicates the number of sachets needed for one day supply preparation of reconstituted oral solution.
[c]The volume of each individual dose, when multiplied by three, may not match the indicated total daily water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

Table 3: Recommended day 14 intermediate dosage 260 mg/kg/day of doxecitine and 260 mg/kg/day of doxribtimine oral solution preparation and dosing based on body weight

Body weight (kg)	**Daily oral solution preparation**		**Individual dose volume (ml) (administered 3 times per day)**
	Number of sachet(s) for reconstitution[b]	**Water volume (ml)[a]**	
3.0 - 3.4	1	40	5.5
3.5 - 3.9			6.5
4.0 - 4.4			7.5
4.5 - 4.9			8
5.0 - 5.9			9.5
6.0 - 6.9			11
7.0 - 7.9			13
8.0 - 8.9	2	80	14
9.0 - 10.4			17
10.5 - 11.9			19
12.0 - 13.9			22
14.0 - 15.9			26
16.0 - 17.4	3	120	29
17.5 - 18.9			30
19.0 - 20.9			35
21.0 - 24.9			40
25.0 - 27.9	4	160	45
28.0 - 31.9			50
32.0 - 34.9			55[c]
35.0 - 37.9	5	200	65
38.0 - 41.9			70[c]
42.0 - 47.9	6	240	75
48.0 - 54.9	7	280	90

55.0 - 61.9	8	320	100
62.0 - 72.9	9	360	115
73.0 - 84.9	10	400	135[c]
85.0 - 92.9	11	440	155[c]
93.0 – 109.9	13	520	175[c]
110.0 – 120.0	15	600	200

[a]Volume of water to reconstitute the powder for the preparation of one day's supply of reconstituted oral solution.
[b]The number indicates the number of sachets needed for one day supply preparation of reconstituted oral solution.
[c]The volume of each individual dose, when multiplied by three, may not match the indicated total daily water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

Table 4: Recommended day 28 maintenance dosage 400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine oral solution preparation and dosing based on body weight

Body weight (kg)	**Daily oral solution preparation**		**Individual dose volume (ml) (administered 3 times per day)**
	Number of sachet(s) for reconstitution[b]	**Water volume (ml)[a]**	
3.0 - 3.4	1	40	9
3.5 - 3.9			10
4.0 - 4.9			12
5.0 - 5.9	2	80	15
6.0 - 6.9			17
7.0 - 7.9			20
8.0 - 8.9			22
9.0 - 10.4			26
10.5 - 11.9	3	120	30
12.0 - 13.9			35
14.0 - 15.9			40
16.0 - 17.4	4	160	45
17.5 - 18.9			50
19.0 - 20.9			55[c]
21.0 - 24.9	5	200	60
25.0 - 27.9			70[c]
28.0 - 31.9	6	240	80
32.0 - 34.9	7	280	90
35.0 - 37.9	8	320	100
38.0 - 41.9			110[c]
42.0 - 47.9	9	360	120
48.0 - 54.9	10	400	140[c]
55.0 - 61.9	12	480	160
62.0 - 72.9	13	520	180[c]
73.0 - 85.0	15	600	210[c]

[a]Volume of water to reconstitute the powder for the preparation of one day's supply of reconstituted oral solution.
[b]The number indicates the number of sachets needed for one day supply preparation of reconstituted oral solution.
[c]The volume of each individual dose, when multiplied by three, may not match the indicated total daily water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

NOTE: There is very limited experience with patients weighing >85 kg. In case of a patient weighing >85.0 kg the total daily volume will exceed 640 ml and **the individual dose** of oral solution should be **prepared three times per day** instead of preparing the solution once per day**.**

When the individual dose volume exceeds 225 ml, it should be divided into two separate portions taken immediately one after the other. The Administration device kit dosing cup must be used to accurately measure and administer each portion.

Table 5: Recommended day 28 maintenance dosage of KYGEVVI oral solution preparation and dosing for patients weighing >85.0 kg

Body weight (kg)	Number of sachet(s) for reconstitution[b]	Water volume (ml)[a]	Individual dose volume (ml) (administered 3 times per day)
85.1 – 92.9	6	240	230
93.0 – 99.9			250[c]
100.0 – 109.9	7	280	270
110.0 – 120.0	8	320	300

[a]Volume of water to reconstitute the powder for the preparation of reconstituted oral solution.
[b]The number indicates the number of sachets needed for preparation of reconstituted oral solution.
[c]The volume of each individual dose may not match the indicated total water volume, this is not an error. Final volume of the reconstituted oral solution will increase after the powder of the prescribed number of sachets is added to the water volume.

If the patient is unable to swallow, the prescribed dose of KYGEVVI can be administered via a feeding tube. Follow the instructions of the feeding tube to administer the medicine.

- Prepare the oral solution using the recommended Administration device kit.
- Dissolve the prescribed number of powder sachets with room temperature water.
  - Use 40 ml of water per sachet.
  - Do not mix with any other medicinal products, liquids, powders or foods.
- Make a one-day supply of oral solution each morning or for a total daily volume exceeding 640 ml for patients weighing >85.0 kg, the solution should be prepared for each individual dose separately.
  - Pour the prescribed amount of water into the mixing bottle first. Then add the powder from the sachets.
  - Close the mixing bottle with the dosing cup, and turn it upside down and back at least 20 times to mix.
  - After administration, store the mixing bottle at room temperature or in the refrigerator.
- Before each administration, turn the mixing bottle slowly upside down and back at least 3 times.

Any remainder after the third dose of the day is taken should be discarded.
For detailed instructions on reconstitution and administration of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Elevated liver enzymes and liver dysfunction/failure have been observed as a clinical manifestation of TK2d. In clinical studies elevations in alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST] have occurred in patients with TK2d following treatment with KYGEVVI. Transaminase levels should be checked prior to initiation of treatment, and changes in liver function monitored periodically during treatment with KYGEVVI and according to routine patient management.

Diarrhoea is a TK2d-related symptom as well as a known undesirable effect of KYGEVVI (see section 4.8). Diarrhoea may be managed according to routine patient management, including anti-diarrhoeals. Based on the severity of the diarrhoea, the dose of KYGEVVI should either be reduced, or

temporarily withheld until diarrhoea improves or returns to baseline, and then resumed gradually (see section 4.2) to a tolerable dose level.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vivo* interaction studies have been performed in adult or paediatric patients. Certain cytotoxic and antiviral medicines (eg, cedazuridine, cisplatin, tipiracil, brivudine, stavudine, ribavarin, fludarabine) may interact with doxecitine and doxribtimine by affecting enzymes that metabolize doxecitine or doxribtimine, or nucleoside transporters. These interactions have not been observed in patients with TK2d treated with doxecitine and doxribtimine; their clinical significance is unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of doxecitine and doxribtimine in pregnant women. Endogenous pyrimidine nucleosides are transported across the placenta by placental nucleoside transporters to help meet the foetal requirements for nucleosides.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
The use of KYGEVVI when planning for and during pregnancy may be considered if the clinical benefit outweighs the risk.

Breast-feeding

It is unknown whether doxecitine and doxribtimine is excreted in human milk, but endogenous pyrimidine nucleosides and nucleotides are present naturally in human milk. At therapeutic doses of KYGEVVI no effects on the breastfed newborns are anticipated. KYGEVVI can be used during breast-feeding.

Fertility

The effect of doxecitine and doxribtimine on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Doxecitine and doxribtimine have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The frequencies of adverse reactions are based on pooled data from clinical studies (MT-1621-101 and TK0102) in 50 patients, who were exposed to KYGEVVI during a median of 78.2 months (min 4, max 157), with a median maintenance dose of 387.2 mg/kg/day of doxecitine and 387.2 mg/kg/day of doxribtimine (min 170; max 400).

The most commonly reported adverse reactions were diarrhoea (86%), vomiting (28%), abdominal pain (including abdominal pain upper) (26%).

Tabulated list of adverse reactions

Adverse reactions (ADRs) from clinical studies are classified by MedDRA System Organ Class and Preferred Term and frequency, using the following convention: 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). The low prevalence of TK2d and the small size of the medicinal product safety database do not allow for detecting adverse reactions that are classified as rare or very rare.

Table 6: Tabulated list of adverse reactions

System organ class	Frequency	Adverse reaction
Gastrointestinal disorders	Very common	Diarrhoea, Vomiting, Abdominal pain (including abdominal pain upper)

Description of selected adverse reactions

Gastrointestinal disturbances
Gastrointestinal disturbances such as diarrhoea, vomiting, and abdominal pain (including abdominal pain upper) are very commonly reported adverse reactions with doxecitine and doxribtimine treatment. In the pooled safety population 37 out of 50 participants (74%) experienced diarrhoea early after treatment initiation (<3 months). The majority of events of diarrhoea were mild to moderate in severity, and were generally self-limiting or improved with temporary dose reduction. Of 133 events of diarrhoea, 12% (16/133) required dose reduction with a median duration of 80 days (Q1, Q3=33.0, 201.5). None of the 50 participants discontinued due to gastrointestinal disturbances, including diarrhoea.

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

There are no data on symptoms associated with an overdose.
Doses of 130 mg/kg/day of doxecitine and 130 mg/kg/day of doxribtimine titrated up to a maintenance dose of 400 mg/kg/day of doxecitine and 400 mg/kg/day of doxribtimine with an intermediate dose of 260 mg/kg/day of doxecitine and 260 mg/kg/day of doxribtimine have been administered in 3 equal daily doses in clinical studies without dose limiting toxicity.
In the event of overdose, it is recommended that the patients are monitored closely for any signs and symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other alimentary tract and metabolism products, various alimentary tract and metabolism products, ATC code: A16AX29

Mechanism of action

The primary mechanism of action of doxecitine and doxribtimine is the incorporation of nucleosides deoxycytidine (dC) and deoxythymidine (dT) into skeletal muscle mitochondrial deoxyribonucleic acid (DNA) to restore mitochondrial DNA copy number and improve skeletal muscle function in patients with TK2d. Doxecitine and doxribtimine likely utilize residual TK2 activity as well as cytosolic phosphorylation pathways such as thymidine kinase 1 and deoxycytidine kinase to increase mitochondrial DNA precursors deoxycytidine triphosphate and deoxythymidine triphosphate in the mitochondria.

Pharmacodynamic effects

No formal pharmacodynamic studies have been conducted with doxecitine and doxribtimine. Effects of doxecitine and doxribtimine on cardiac electrophysiology have not been determined in a formal clinical trial because doxecitine and doxribtimine are chemically identical to ubiquitous endogenous nucleosides.

Clinical efficacy

Data from two clinical studies (MT-1621-101 and TK0102) were pooled to study the efficacy and safety of doxecitine and doxribtimine in patients with genetically confirmed TK2d.

MT-1621-101, a retrospective chart review study, collected data on 38 treated paediatric and adult study participants with TK2d who were treated with pyrimidine nucleos(t)ides. TK0102 is an open-label, single arm clinical study in participants with TK2d previously treated with pyrimidine nucleos(t)ides. A total of 47 study participants enrolled in TK0102; 35 originated from MT-1621-101. After enrolment in Study TK0102, study participants started treatment with (or switched to) doxecitine and doxribtimine.

Together, MT-1621-101 and TK0102 comprise 39 participants with an age of TK2d symptom onset ≤12 years. A total of 26 patients (67%) were male; median age of TK2d symptom onset was 1.89 years (Q1,Q3 = 1.2, 2.7) and the median duration of treatment was 91.4 months (Q1, Q3=80.2, 117.8; all treated >5 years).

Developmental motor milestones, ventilatory support, and feeding support were compared pre- and post-treatment.

Motor milestones
Pre- and posttreatment developmental motor milestone loss and regain for the MT-1621-101 + TK0102 treated population subgroup with an age of TK2d symptom onset ≤12 years is summarized in Table 7.

Table 7: Developmental motor milestones lost and regained, age of TK2d symptom onset ≤12 years, MT-1621-101 + TK0102 evaluable population

	LOST		**REGAINED**	
	Before treatment start [(a)]	**After treatment start** [(b)]	**Before treatment start**[(c)]	**After treatment start**[(d)]
≥1 milestone abilities	32/39 (82.1%)	10/38 (26.3%)	1/32 (3.1%)	26/31 (83.9%)
Developmental motor milestone ability				
Hold head upright, unassisted	16/39 (41.0%)	1/38 (2.6%)	0/16	15/17 (88.2%)
Sit upright, unassisted	13/38 (34.2%)	1/36 (2.8%)	0/13	10/14 (71.4%)
Stand, assisted	13/36 (36.1%)	3/31 (9.7%)	0/13	8/15 (53.3%)
unassisted	14/34 (41.2%)	4/29 (13.8%)	0/14	7/15 (46.7%)
Walk, assisted	15/36 (41.7%)	3/30 (10.0%)	0/15	9/16 (56.3%)
unassisted	15/34 (44.1%)	1/27 (3.7%)	0/15	6/16 (37.5%)
Climb stairs, assisted	18/31 (58.1%)	2/26 (7.7%)	0/18	9/19 (47.4%)
unassisted	16/19 (84.2%)	0/20	0/16	6/16 (37.5%)
Run	17/21 (81.0%)	2/20 (10.0%)	1/17 (5.9%)	7/17 (41.2%)

[(a)] For the pre-treatment summary, the denominator represents the number of participants that initially acquired a developmental motor milestone in the pre-treatment period.
[(b)] For the post-treatment summary, the denominator represents the number of participants that initially acquired a developmental motor milestone pre-treatment and did not lose it pre-treatment or acquired a developmental motor milestone post-treatment.
[(c)] The denominator represents the number of participants that initially acquired a developmental motor milestone and lost that milestone in the pre-treatment period.
[(d)] The denominator represents the number of participants that lost a developmental motor milestone pre-treatment and did not regain it pre-treatment or lost a developmental milestone post-treatment.

Ventilatory and feeding support
In the MT-1621-101 + TK0102 treated population with an age of TK2d symptom onset ≤12 years, prior to treatment start, 18/39 (46%) participants initiated ventilatory support and no participants discontinued ventilatory support. After initiation of treatment, 5/21 (24%) participants started ventilatory support while 5/23 (22%) discontinued ventilatory support.
With regard to feeding support, prior to treatment start, 12/39 (31%) participants had a feeding tube. After initiation of treatment, 4/28 (14%) participants started feeding support, with 2 of these participants subsequently discontinuing feeding support after initiation of treatment.

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 the SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of doxecitine and doxribtimine have been studied in healthy volunteers, in participants with moderate and severe renal impairment, and in paediatric and adult participants with TK2d.The pharmacokinetics of doxecitine and doxribtimine were characterized by moderate to high intra- and inter-subject variability.

Absorption

The absolute oral bioavailability of doxecitine and doxribtimine in humans is not known, but is anticipated to be low (< 10%). After oral administration of doxecitine and doxribtimine, mean peak concentrations (C_{max}) of dC and dT are achieved within approximately 1.5 hours (T_{max}) in the fasted state. Systemic exposures (baseline-adjusted C_{max} and AUC_{0-t}) following increasing single oral doses of doxecitine and doxribtimine (86.6 mg/kg, 173.4 mg/kg, and 266.6 mg/kg) in healthy volunteers increase in a less than dose proportional manner for dC (geometric mean [%geoCV] AUC_{0-t} values of 13.49 [94.1], 23.23 [66.7], and 30.79 [76.5] ng*hr/ml, respectively) and in a more than dose proportional manner for dT (geometric mean [%geoCV] AUC_{0-t} values of 12.56 [124.9], 31.71 [126.6], and 91.15 [94.1] ng*hr/ml, respectively).

Administration of 266.6 mg/kg doxecitine and doxribtimine with a high-fat, high-calorie meal increased baseline-adjusted C_{max} and AUC_{0-t} by 79% and 137%, respectively, for plasma dC, and by 27% and 74%, respectively, for plasma dT compared with the fasted state, confirming a significant food effect. The high fat and high-calorie meal tended to prolong the T_{max} of dC and dT to median values of 2.02 h for dC and 4.00 h for dT, respectively.
KYGEVVI should be taken with food to ensure higher bioavailability of doxecitine and doxribtimine, and to minimize PK variability due to inconsistent dosing in fed and fasted states.

Distribution

Plasma protein binding of doxecitine and doxribtimine is relatively weak (less than 10% bound).

Biotransformation

Deoxycytidine and dT are primarily degraded (catabolized) by cytidine deaminase and thymidine phosphorylase, respectively, to the nucleobases and the 2-deoxy-α-D-ribose 1-phosphate moiety. Intermediate products of deoxycytidine catabolism are deoxyuridine, uracil and dihydrouracil with the end products β-alanine, ammonia, and CO_2. Thymine, the pyrimidine nucleobase of deoxythymidine, is subsequently catabolized to dihydrothymine and ultimately to γ-amino-isobutyric acid and CO_2. Doxecitine and doxribtimine are not substrates of known CYP enzymes.

Elimination

Mass balance of dC and dT following oral administration of doxecitine and doxribtimine has not been determined. Hepatic and extrahepatic metabolism is considered to be the main pathway for clearance of dC and dT at plasma concentrations relevant to the proposed dose range of doxecitine and doxribtimine.

Urinary excretion of intact dC and dT is exceedingly low (<1% of dose) in healthy volunteers following single oral administration of doxecitine and doxribtimine. However, taking into account the anticipated low oral bioavailability, renal elimination could be more pronounced. Renal elimination of unchanged dC and dT is likely a minor pathway in the proposed dose range.

Special populations

Based on population pharmacokinetic analysis, age (range: 0.8 to 81 years), sex, and race were not significant covariates of variability in the pharmacokinetics of doxecitine and doxribtimine; age was a significant covariate of the estimated baseline plasma concentrations of dT. No dose adjustments for age, sex or race are recommended.

Renal impairment
In a dedicated clinical study, renal impairment was associated with a substantial increase in systemic exposures (C_{max}, AUC_{0-t}) of dC and dT following a single oral administration of 266.6 mg/kg doxecitine and doxribtimine (133.3 mg/kg doxecitine and 133.3 mg/kg doxribtimine) in adult non-TK2d volunteers with moderate (eGFR between ≥30 and ≤59 ml/min/1.73 m^2) or severe (eGFR ≥15 and ≤29 ml/min/1.73 m^2) renal impairment when compared with matched healthy volunteers with normal renal function. Systemic exposures to dC and dT were characterized by high inter-subject variability. Baseline-adjusted plasma dC AUC_{0-t} (geometric mean) was 122% (56.4 vs. 25.4 ng*hr/ml) and 66% (52.8 vs. 31.8 ng*hr/ml) higher in participants with moderate and severe renal impairment, respectively, compared with matched healthy study participant control groups. Baseline-adjusted plasma dT AUC_{0-t} (geometric mean) was 447% (23.7 vs. 4.34 ng*hr/ml) and 148% (31.5 vs. 12.7 ng*hr/ml) higher in participants with moderate and severe renal impairment, respectively, compared with healthy matched participants. Urinary excretion of intact dC and dT was low (<1% of dose) in all groups. However, the absolute oral bioavailability is anticipated to be low and therefore the influence of kidney function may be underestimated based on urinary excretion data alone.

Hepatic impairment
No specific study has been conducted to evaluate the pharmacokinetics of doxecitine and doxribtimine in hepatic impairment.

Paediatric population
Paediatric participants with TK2d in the clinical program were administered doxecitine and doxribtimine with the same dosing regimen (based on body weight) as in adults. Systematic differences in exposures to dC and dT were not apparent between paediatric and adult participants when considering interindividual variability and limited number of participants. An impact of maturation processes in the metabolic pathways cannot be excluded.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development, and juvenile toxicity.

Increased incidence of distended aorta, narrow pulmonary trunk, misshapen sternebrae, incompletely ossified sternebrae, and incompletely ossified cervical centra were observed in the offspring of rabbits. However, these malformations and skeletal variations were observed at exposures much in excess of the maximum human exposure and occurred only in foetuses born from dams with maternal toxicity. Furthermore, no embryofoetal toxicity was found in rats. Therefore, these effects are considered of little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

6.2 Incompatibilities

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

6.3 Shelf life

30 months.

After reconstitution

Do not store above 25°C. Can be stored in a refrigerator (2°C – 8°C). Do not freeze.
If not used within 16 hours, the oral solution should be discarded.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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

6.5 Nature and contents of container

Laminated foil sachet made of PET/Alu/low density polyethylene.

Pack size of 30 sachets.

6.6 Special precautions for disposal and other handling

Preparation

- Prepare doxecitine and doxribtimine oral solution at room temperature.
- Use the mixing bottle and cup (the “dosing system”) provided in the Administration device kit.
- Dissolve the prescribed number of powder sachets with room temperature water.
  - Each sachet contains 2 g of doxecitine and 2 g of doxribtimine.
  - Use 40 ml of water per sachet.

- Make a one-day supply of oral solution each morning or for a total daily volume exceeding 640 ml for patients weighing >85.0 kg, the solution should be prepared for each individual dose separately.
  - Pour the prescribed amount of water into the mixing bottle first. Then add the powder from the sachets.
  - Close the mixing bottle with the dosing cup, and turn upside down and back at least 20 times to mix.
- Once prepared, the oral solution should be ingested within 16 hours.
- Before each administration, turn the mixing bottle slowly upside down and back at least 3 times.
- Discard any remainder after the third dose of the day is taken.

Feeding tubes
KYGEVVI reconstituted oral solution is compatible with the most commonly available feeding tubes (polyurethane, polyvinyl chloride, silicone) from size 4 French and up, with a maximum length of 125 cm. To flush the tube, a single flushing step with a volume of water equivalent to the tube's priming volume is sufficient. Follow the instructions of the feeding tube to administer the medicine.

The reconstituted solution is opalescent and colourless and can have some powder residue at the bottom or top.

See Instructions for Use provided at the end of the Package Leaflet.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2013/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

DD/MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

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

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.

An updated RMP shall be submitted by {CHMP agreed deadline}.

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
Non-interventional post-authorisation safety study (PASS): TK0109: to describe the safety and clinical outcomes of doxecitine and doxribtimine treatment in patients with thymidine kinase 2 deficiency (TK2d) with age of symptom onset on or before 12 years.	Annually (with annual re-assessment)
In order to ensure adequate monitoring of safety and efficacy of Kygevvi in the treatment of patients with thymidine kinase 2 deficiency (TK2d), the MAH shall provide yearly updates on any new information concerning the safety and efficacy of Kygevvi.	Annually (with annual re-assessment)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

KYGEVVI 2 g/2 g powder for oral solution
doxecitine/doxribtimine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 2 g of doxecitine and 2 g of doxribtimine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral solution
30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use after reconstitution.

Push in and lift to open.

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
Reconstituted oral solution: Use within 16 hours.

9. SPECIAL STORAGE CONDITIONS

Reconstituted oral solution: Do not store above 25°C. Can be stored in a refrigerator. Do not freeze.

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

UCB Pharma S.A. (logo)
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/2013/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kygevvi 2 g/2 g

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

SACHET

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

KYGEVVI 2 g/2 g powder for oral solution
doxecitine/doxribtimine
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

KYGEVVI 2 g/2 g powder for oral solution
doxecitine/doxribtimine

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

Read all of this leaflet carefully before you start taking 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, pharmacist or nurse.
- 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.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KYGEVVI is and what it is used for

KYGEVVI contains the active substances doxecitine and doxribtimine. KYGEVVI is known as nucleosides therapy.

KYGEVVI is used in children and adults in whom disease symptoms started on or before 12 years of age to treat thymidine kinase 2 deficiency (TK2d), a rare form of inherited mitochondrial DNA depletion and deletion syndrome.
Mitochondria are parts of the cell that produce the cell's energy and they carry their own genetic material called mitochondrial DNA. TK2d is caused by mutations (changes) in a gene called TK2 which provides instructions for making a protein known as thymidine kinase 2. This protein helps mitochondria function properly. Mutations in the TK2 gene result in production of a faulty protein. As a result, the mitochondria can't make enough copies of their own DNA, leading to a gradual loss of energy in patients with TK2d. TK2d mainly affects the muscles, causing weakness, especially in the muscles used for movement, breathing and swallowing.

2. What you need to know before you take KYGEVVI

Do not take KYGEVVI
- if you are allergic to any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before taking KYGEVVI if:
- You have or have had liver problems because increase in liver function tests can occur during KYGEVVI treatment. Your doctor will check your liver both before and during treatment with KYGEVVI.
- You have diarrhoea, as your doctor may need to adjust your dose.

Other medicines and KYGEVVI
Tell your doctor or pharmacist if you are taking, have recently used or might use any other medicines. In particular, tell your doctor, pharmacist or nurse 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)

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

The effects of KYGEVVI in pregnancy are not known, so do not take this medicine if you are pregnant or think that you may be pregnant unless your doctor specifically recommends it.

If you plan to breast-feed, ask your doctor or pharmacist for advice before taking this medicine. This is because it is not known whether the medicine passes into human breastmilk although no effects on the baby are expected.

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

3. How to take KYGEVVI

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 management of mitochondrial disorders.

Dosing KYGEVVI
- The dose of KYGEVVI 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 adjust your dose depending on how well you tolerate it.
- 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.

Prepare KYGEVVI
- Use the recommended dosing system (mixing bottle and cup) to prepare the reconstituted oral solution.
- KYGEVVI must only be prepared with room temperature water (between 15°C to 25°C).
- Do not mix KYGEVVI 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 KYGEVVI.

Take KYGEVVI
- By mouth (oral) 3 times a day in equally divided doses, approximately 6 hours apart ±2 hours,
- You should take KYGEVVI with food.
- If a dose is missed or if you are not sure you took all of the medicine, do not take another dose. Wait until the next scheduled dose.
- If necessary, this medicine may be given via a feeding tube with or after a feed (see section "Use of feeding tube").

Use of feeding tube
- KYGEVVI oral solution is compatible with most commonly available feeding tubes (polyurethane, polyvinyl chloride, silicone) from 4 French and up with a maximum length of 125 cm.
- Be sure KYGEVVI is given with or after a feed.
- If you take or give KYGEVVI via a feeding tube, ensure you follow manufacturer's instructions. For more information, ask your doctor, pharmacist or nurse.

If you take more KYGEVVI than you should
If you suspect that you have accidentally taken a higher dose of KYGEVVI than prescribed, please contact your doctor for advice, as soon as possible.

If you forget to take KYGEVVI
If you miss a dose, you should take the dose as soon as you remember. However, if it is within 2 hours of the next planned dose, skip the missed dose and take the next dose at the usual time. A double or extra dose should not be taken to make up for a missed dose.

If you stop taking KYGEVVI
Interrupting or stopping treatment with this medicine may cause your symptoms to come back. Talk to your doctor before stopping KYGEVVI. 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.

4. Possible side effects

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

Very common (may affect more than 1 in 10 people)
- Diarrhoea
- Vomiting (being sick)
- Belly (abdominal) pain

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via 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 KYGEVVI

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 sachet and carton after “EXP”. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.

Reconstituted solution
After reconstitution, the solution should be used within 16 hours.
Do not store above 25°C. Can be stored in a refrigerator (2°C and 8°C). Do not freeze.

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 KYGEVVI contains
- The active substances are doxecitine and doxribtimine. One sachet contains 2 g of doxecitine and 2 g doxribtimine.
- The other ingredients are silica colloidal anhydrous (E551), magnesium stearate (E470b).

What KYGEVVI looks like and contents of the pack
KYGEVVI is a white to off-white powder for oral solution, supplied in a sachet. Each carton contains 30 sachets.

Marketing Authorisation Holder
UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
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Manufacturer
Catalent Germany Schorndorf GmbH
Steinbeisstrasse 1-2
Schorndorf, Baden-Württemberg, 73614
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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UCB s.r.o., organizačná zložka
Tel: + 421 (0) 2 5920 2020

Suomi/Finland
UCB Pharma Oy Finland
Puh/Tel: + 358 9 2514 4221

Sverige
UCB Nordic A/S
Tel: + 46 / (0) 40 294 900

This leaflet was last revised in

Other sources of information

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

Instructions for Use

Table of contents

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**).

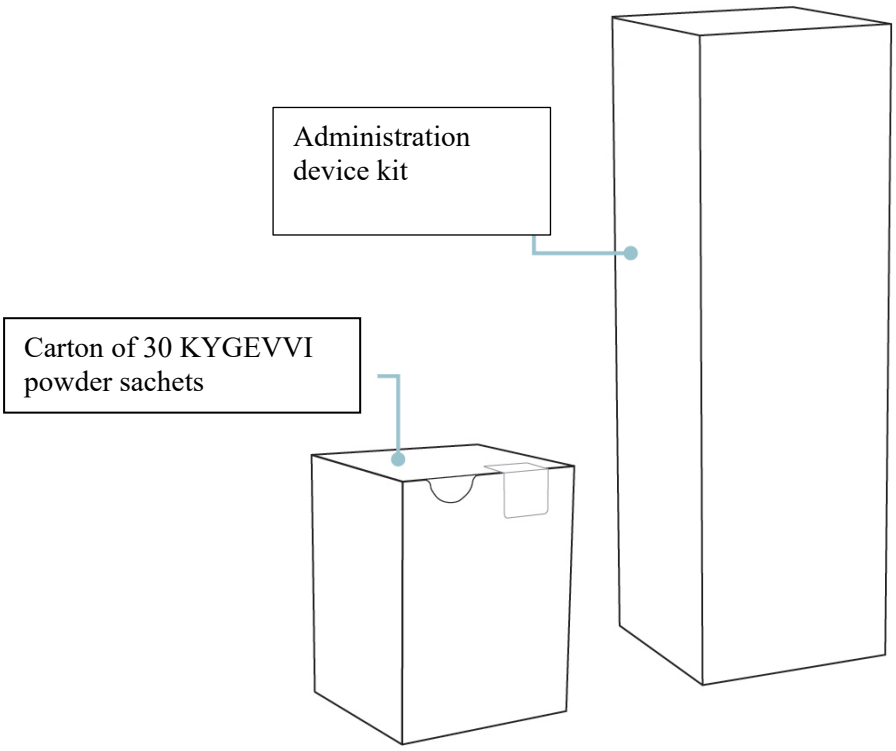
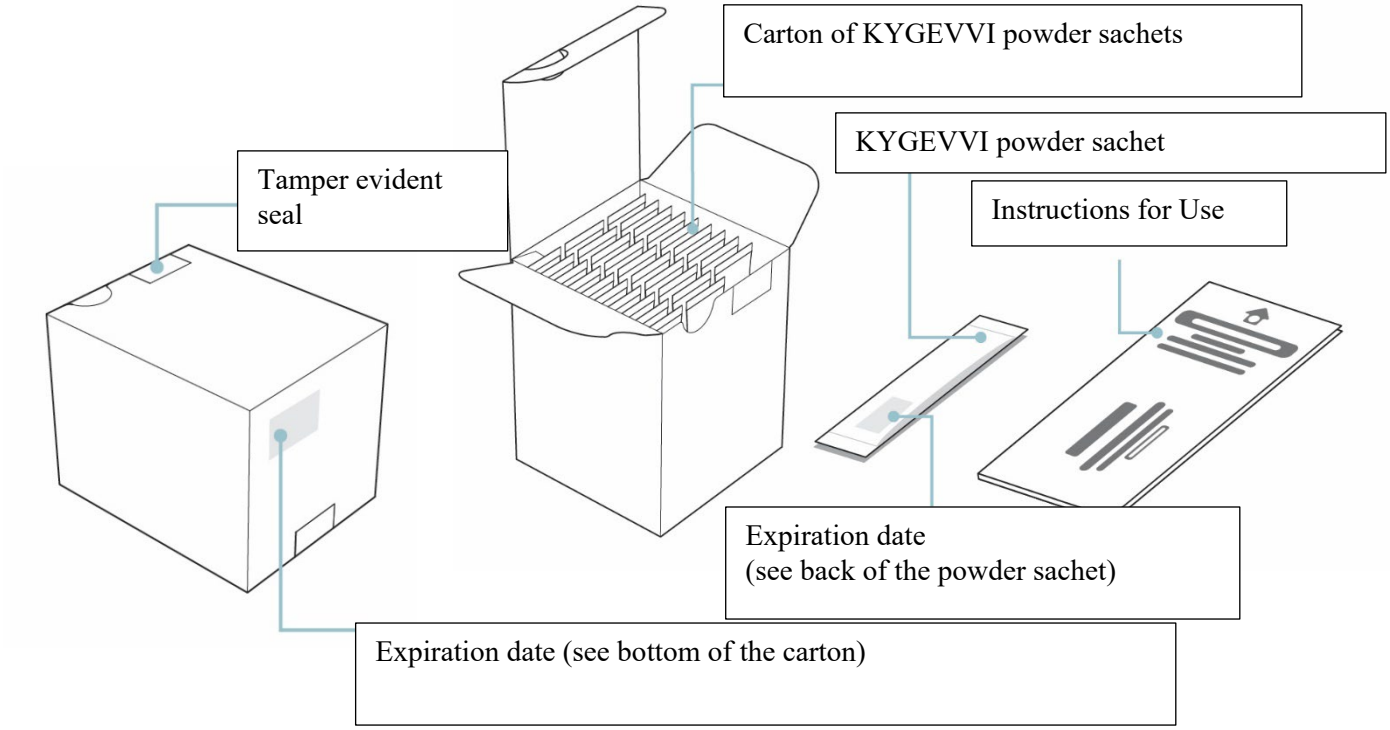


Figure A

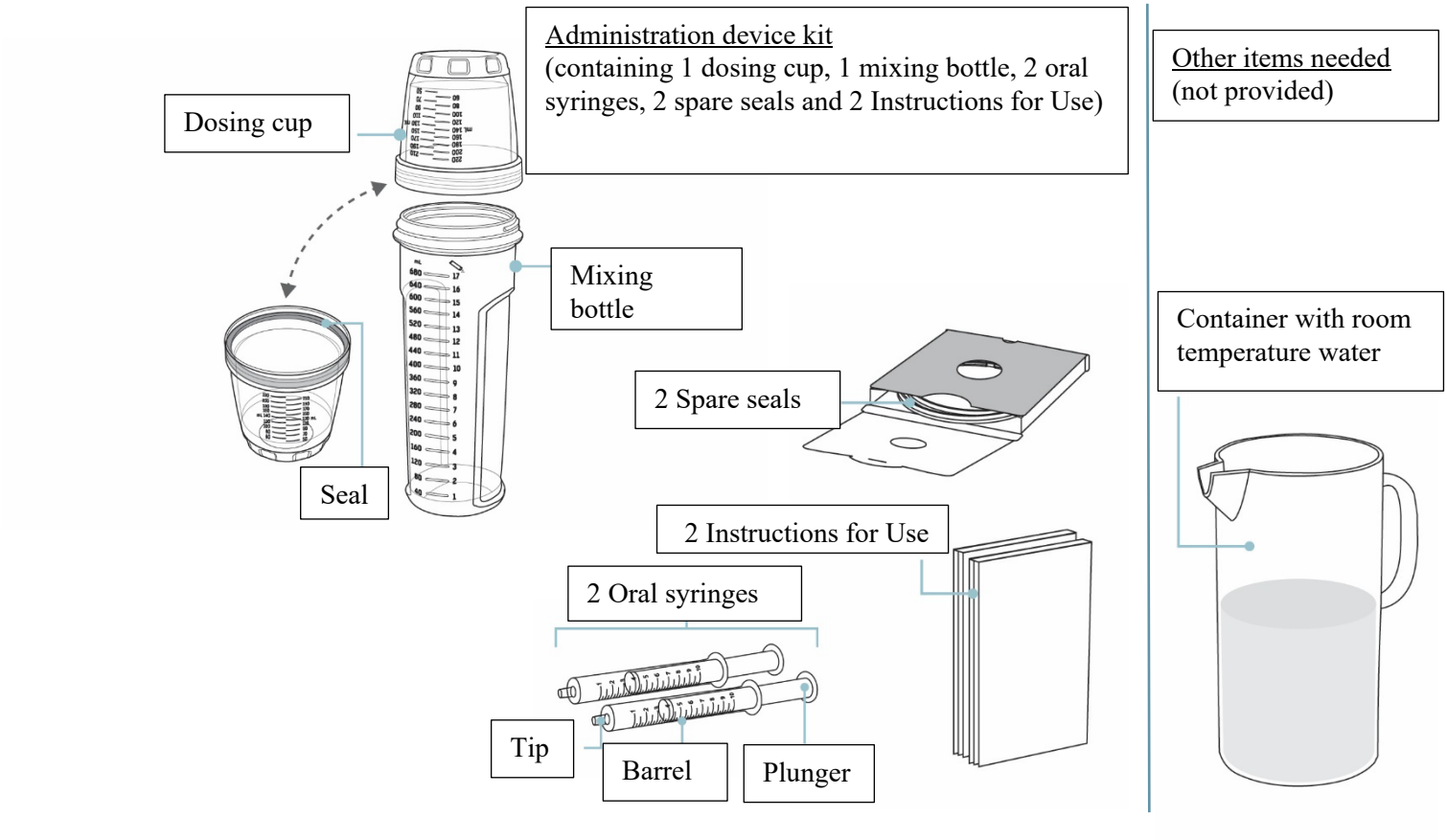
Before you start

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

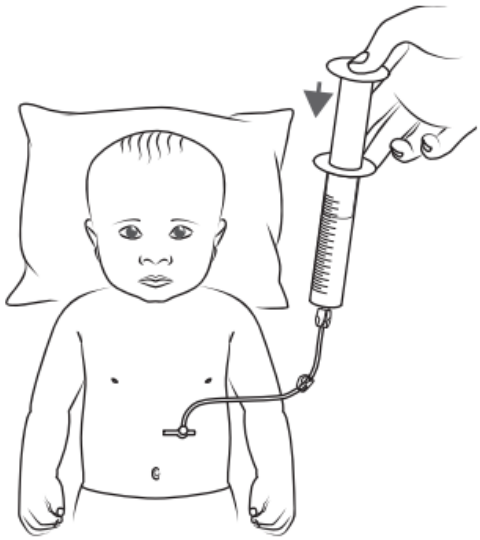


Important information

What you need to know before 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.

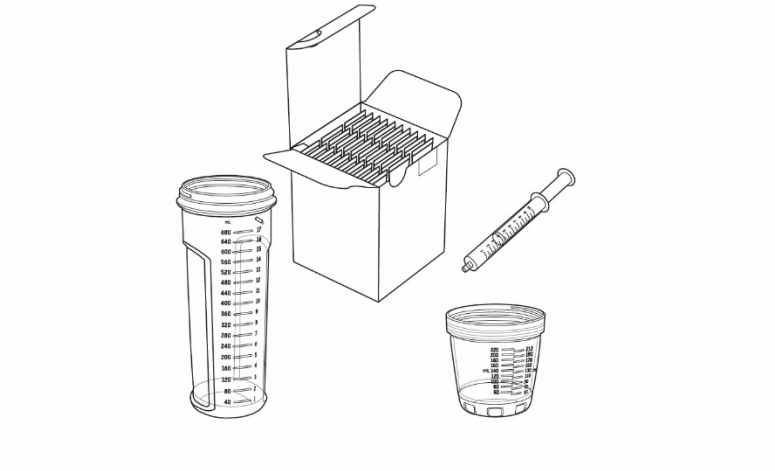


Figure B

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)**.

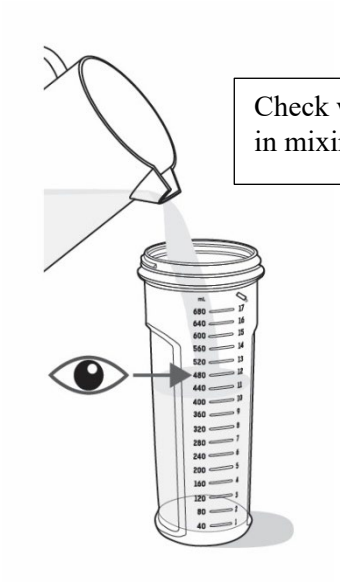
c) Check you have counted out the correct number of KYGEVVI powder sachets for your one-day supply, as shown on your prescription.

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.



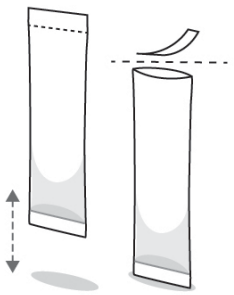


Figure C **Figure D** **Figure E** **Figure F**

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

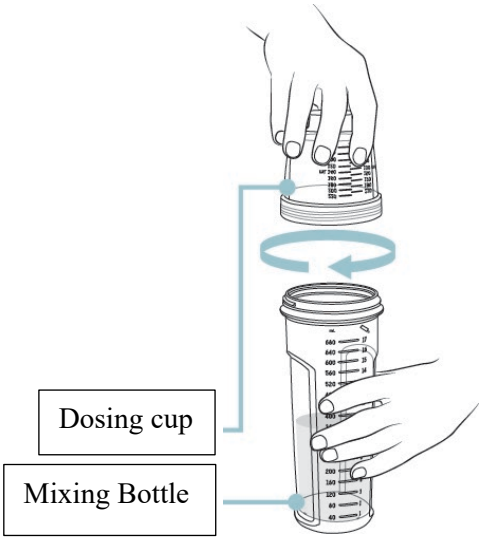


Figure H

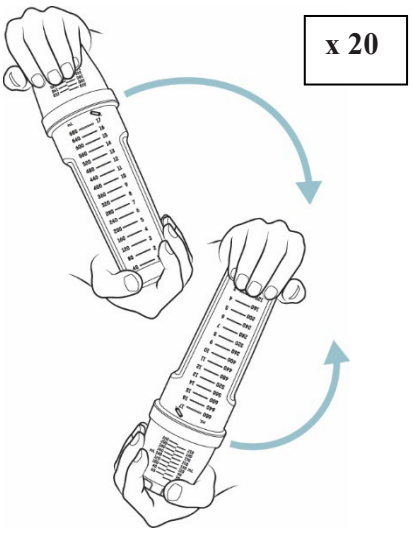
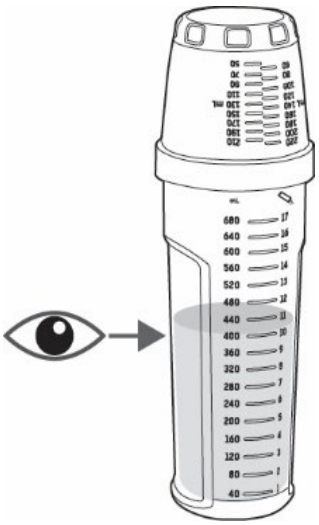


Figure I



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

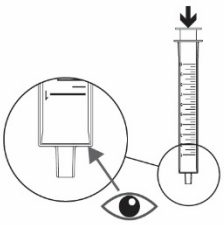


Figure M

Figure N

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**).

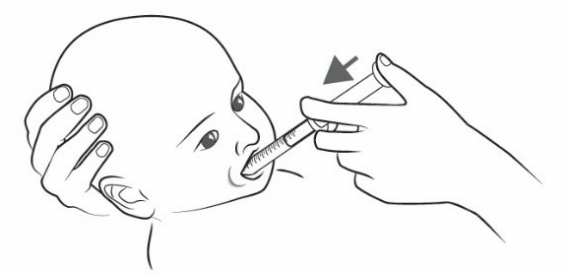


Figure O

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

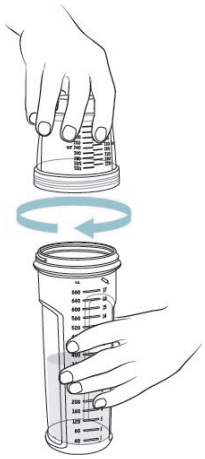


Figure Q

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

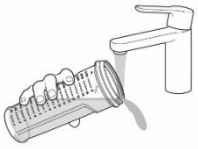


Figure T

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

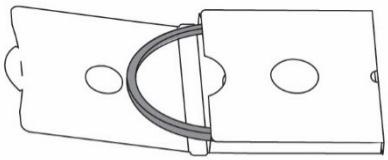


Figure X

Figure Y

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

Annex IV

Conclusions on the granting of the marketing authorisation under exceptional circumstances presented by the European Medicines Agency

Conclusions presented by the European Medicines Agency on:

- **Marketing authorisation under exceptional circumstances**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the marketing authorisation under exceptional circumstances as further explained in the European Public Assessment Report.