22 April 2021
EMA/300397/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Akynzeo

fosnetupitant / netupitant / palonosetron

Procedure no: EMEA/H/C/003728/P46/004.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 25 August 2020, the MAH submitted a completed paediatric study (NEPA-15-31) for Akynzeo 300mg Netupitant/0.5mg Palonosetron hard capsules, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This application was assessed as part or Procedure EMA/H/C/003728/P46/0004.

Following the initial assessment of that submission, two questions remained for the applicant to address, namely the characterisation of the safety profile of the excipients used in the product with respect to their use in children below the age of 3 years, and confirmation that two patients in the study had indeed received the correct dose of the product in the clinical trials.

Following on from this, the Applicant has submitted this application to clarity these remaining issues. As such, this report should be considered in the context of the original application.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that NEPA-15-31, A multicentre, multinational, randomized, double-blind, pharmacokinetic and pharmacodynamic (PK/PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in paediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy is part of an ongoing paediatric clinical development program in accordance with Paediatric Investigation Plan, EMEA-001198-PIP03-17.

2.2. Information on the pharmaceutical formulation used in the study

The 3 investigational medicinal products (IMPs) used during the study are shown below:

Identity of Investigational Medicinal Products

Name:	**Oral Netupitant (IMP 1)**
Dosage form:	Glass vial with liquid formulation (suspension)
Strength:	100 mg netupitant / 7 mL
Dosing:	Netupitant was administered based on BW as a single oral dose 1 hour (±10 minutes) prior to the start of emetogenic chemotherapy on Day 1
Route of administration:	Oral
Name:	**Oral Netupitant (IMP 2)**
Dosage form:	Glass vial with liquid formulation (suspension)
Strength:	300 mg netupitant / 7 mL
Dosing:	Netupitant was administered based on BW as a single oral dose 1 hour (±10 minutes) prior to the start of emetogenic chemotherapy on Day 1
Route of administration:	Oral
Name:	**Oral Palonosetron (IMP 3)**
Dosage form:	Glass vial with liquid formulation (solution)
Strength:	0.75 mg palonosetron / 5 mL (oral administration of the 0.75 mg/5 mL solution for IV use)
Dosing:	Palonosetron was administered based on BW at the dosage of 20 µg/kg (up to a maximum of 1.5 mg for patients weighing ≥75 kg), immediately (within 5 minutes) after netupitant, i.e., 1 hour (±10 minutes) prior to start of emetogenic chemotherapy on Day 1
Route of administration:	Oral

Abbreviations: BW = body weight; IMP = investigational medicinal product; IV = intravenous.

2.3. Clinical aspects

2.3.1. Introduction

The MAH originally submitted a final report for:

- NEPA-15-31, A multicentre, multinational, randomized, double-blind, pharmacokinetic and pharmacodynamic (PK/PD) dose-finding study of oral netupitant administered concomitantly with oral palonosetron in paediatric cancer patients for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

At the conclusion of the original assessment, the CHMP was satisfied that the Post-authorisation measure had been fulfilled. However, there remained some aspects of the application which required further clarification, these were put to the applicant as follows;

Some minor points remain, primarily relating to the clarification of the safety profile of the excipients chosen for use in paediatric patients below the age of 3 years, and the exceptionally high exposure seen in two younger patient receiving the lower (1.33mg/Kg) netupitant dose.

The applicant is requested to provide a more detailed description of the safety profile of the excipients used, with particular regard to patients below the age of 3 years, as it is not clear whether the established safety profile of these substances in older children can be reliably extrapolated into this population (OC)

The applicant is asked to confirm that patient #101168 and #301141 both received the correct dose, and if so discuss the possible reasons for the exceptionally high Cmax seen in those patients. (OC)

The applicant has reverted with additional clarifications regarding these two remaining questions.

2.3.2. Clinical study

Please see the parent procedure EMA/H/C/003728/P46/0004 for details on the clinical study originally submitted as aprt of the now-fulfilled post-authorisation measure.

As regards the two outstanding issues, the response of the applicant and the assessor's comments therein are summarised below.

Question 1

The applicant is requested to provide a more detailed description of the safety profile of the excipients used, with particular regard to patients below the age of 3 years, as it is not clear whether the established safety profile of these substances in older children can be reliably extrapolated into this population (OC)

Summary of Applicant's Response

The applicant has further investigated the available information for each excipients used in the IMPs formulation in order to provide more detailed description. Reference has been made to the existing safety data from adult human and paediatric population and the corresponding use data in order to perform a comprehensive safety assessment including the safety concerns and risk from the use of the chosen excipients in the overall paediatric population.

Several sources of information have been used including publications and guidances, national databases related to approved drug products (dailymed, eMC, EMA), approved drug product excipients (FDA inactive ingredients database) and regulations on food additives and flavoring (e.g., EFSA Scientific Assessments, Joint Expert committee on food additives (JECFA); US FDA GRAS list) to determine the safety profile of these substances and the risks for all the paediatric age groups with a focus on the youngest ones (e.g. age below 3 years or age groups below 5 years).

The applicant is also aware that a reference list on excipients generally considered safe for use in paediatric formulations is not available yet and therefore this was a rationale for selecting only compendial grade excipients recognized as safe (GRAS) and extensively used in children, taking into account that excipients are necessary ingredients of drug products particularly in oral paediatric formulations where taste remains a key aspect to ensure compliance and the delivery of the therapeutic dose; this also combined to the need to limit the number and amount of each excipient to the minimum necessary.

As first step, an evaluation has been performed on the broad use of all the excipients chosen for Netupitant Paediatric Oral Suspension in pharmaceutical oral dosage forms for approved drug products, their Maximum Daily Exposure (MDE) or, when this is not specified, the Maximum Potency per unit dose (data are from FDA inactive ingredients database). A summary is presented in Table 1 below.

The most commonly used excipients are polyalcohol such as Glycerin and Sorbitol for which MDEs of 31536 mg (for solutions) and 45000 mg (for suspension) oral dosage forms) are reported, respectively.

For these ingredients (except for potassium sorbate) an acceptable daily intake (ADI) level has been specified which is the safest category possible.

Among other excipients the lowest MDEs are reported for Potassium Sorbate (120 mg) and Xanthan Gum (184 mg), while those related to Citric Acid and its tribasic salt (510 mg and 984 mg, respectively) are specified for Intravenous Injection only.

Table 1: Common oral dosage forms and Excipients Maximum Daily Exposure (MDE)

Dosage forms	Glycerin 98%	Xanthan Gum	Potassium Sorbate	Citric Acid Anhydrous[2]	Sodium Citrate Tribasic[2]	Sorbitol[1]
Total Number dosage forms per route (usage)	80	32	19	55	45	62
Any forms MDE	**31536 mg**	**184 mg**	**120 mg**	**510 mg**	**984 mg**	**45000 mg**
Common oral dosage forms	**MDE** (Max. Potency per dose unit)	**MDE** (Max. Potency per dose unit)	**MDE** (Max. Potency per dose unit)	**MDE** (Max. Potency per dose unit)	**MDE** (Max. Potency per dose unit)	**MDE** (Max. Potency per dose unit)
Capsule	**1379 mg** (NR)	**NA** (0.01mg)	**NA** (NR)	**NA** (32.7mg)	**NA** (17.42mg)	**672mg** (NR)
Concentrate	**NA** (750mg/1ml)		**NA** (0.1mg/1ml)	**12mg** (NR)		**NA** (600mg/1ml)
Granule for Suspension		**180 mg** (NA)	**NA** (20mg/5ml)	**NA** (4.9mg)		**NA** (28mg/5ml)
Liquid	**NA** (936.75mg/5ml)			**NA** (2mg/1ml)		**NA** (2970mg/5ml)
Liquid Extended Release		**NA** (4.17mg/1ml)		**NA** (5.18mg/1ml)		
Powder for Suspension		**NA** (360mg)	**NA** (NR)	**360 mg** (NR)	**NA** (501mg/5ml)	**8571 mg** (NR)
Suspension	**15000 mg** (NR)	**NA** (300mg/5ml)	**120 mg** (NR)	**128 mg** (NR)	**180 mg** (NR)	**45000 mg** (NR)
Powder		**NA** (275mg)				**NA** (0.05mg)
Suspension Extended Release	**800 mg** (NR)	**NA** (186.8mg)				
Powder for Solution		**NA** (10mg/5ml)		**NA** (12.25mg)		
Solution	**31536 mg** (NR)	**NA** (1.5mg/1ml)	**NA** (1000mg/15ml)	**244 mg** (NR)	**NA** (18.5mg/1ml)	**12000 mg** (NR)
Syrup	**NA** (1650mg/5ml)		**NA** (2mg/1ml)	**NA** (22.32mg/5ml)	**NA** (58.71mg/5ml)	**NA** (4370mg/5ml)

[1]Sorbitol Syrup n.c. 70%

[2] Citric Acid Anhydrous and Sodium Citrate Tribasic MDE are specified for Intravenous Injection and

NA = a Maximum daily Exposure (MDE) has not been specified for the intended dosage form; NR = Max. Potency per dose unit not reported

The excipient is not used for this oral dosage

In addition to the information available on the level of excipients in oral dosage forms approved for human medicines and their MDE, a brief summary of the dosage or exposure level from literature or food additives and flavoring regulations is summarized below for each excipient since they are all also commonly used as food additives for the overall population including children and elderly.

Glycerol

In a study [Peltola et al, 2007], oral administration of 85% glycerol given for 48 h at a dosage of 1.5 g (1.5 mL) per kg every 6 h in children aged from 2 months through 16 years was considered safe. The EFSA recently conducted a re-evaluation of glycerol (E 422) as a food additive; the Panel stated that glycerol has low acute toxicity and did not raise concern with regards to genotoxicity and carcinogenicity. The Panel conservatively considered the lowest oral dose of glycerol required for

therapeutic effect to be 125 mg/kg bw (body weight) per hour and noted that infants and toddlers can be exposed to that dose by drinking less than the volume of one can (330 mL) of a flavoured drink. The Panel further concluded that the acute bolus exposure to glycerol by its use as a food additive should stay below doses at which pharmacological or side effects could occur and there is no need for a numerical ADI and no safety concern regarding the use of glycerol (E 422) as a food additive at the refined exposure assessment for the reported uses [EFSA, 2017]. The Panel estimated chronic exposure to glycerol (E 422) for the following population groups: infants; toddlers, children, adolescents, adults and the elderly, a summary is provided below.

Table 2 -Summary of exposure to glycerol (E 422) from its use as a food additive

	Infants (12 weeks–11 month)	Toddlers (12–35 month)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Maximum level exposure assessment scenario						
Mean	10–138	158–583	239–480	128–326	68–185	76–138
95th percentile	269–457	484–938	489–910	283–629	161–404	168–268

Source: Table 5 in EFSA re-evaluation of glycerol (E 422) as a food additive.

In this assessment, mean exposure to glycerol ranged from 10 mg/kg bw per day in infants to 583 mg/kg bw per day in toddlers below the age of 3 years.

Sorbitol

Although there is no maximum safe dose for sorbitol, it is suggested that the maximum daily intake should not exceed 20 g/day in adults [Rowe et al, 2006]. The reported side effects of sorbitol, especially when consumed in excessive amounts, in children include diarrhoea, colic and bloating [Jain et al, 1985]. Sorbitol is one of the most prevalent nutrients in fruit juice which often are recommended by paediatricians as a source of vitamin C and an extra source of water for healthy infants and young children [Pediatrics, 2001]. The recommended maximal intake of sorbitol in adults is 20 g/day. Using the weight of an "average" adult male (70 kg) as the denominator, the adult recommendations equate to 2 g of sorbitol/kg body weight/week [Whittaker et al, 2009]. However, it is recognized that over the threshold of 140 mg/kg/day (equivalent of 10 g/70 kg) it can cause laxative effects and gastrointestinal discomfort in adults and paediatric patients as stated in the relevant guideline on the Information in the package leaflet [EMA/CHMP/460886/2014].

Xanthan gum

In 2017 EFSA performed a safety review on xanthan gum as a food additive. The Panel concluded that there is no need for a numerical ADI for xanthan gum (E 415) and no safety concern at the refined exposure assessment for the reported uses and use levels of xanthan gum as a food additive. It is reported that repeated oral intake by adults of large amounts of xanthan gum up to 15,000 mg/person per day, corresponding to 214 mg/kg bw per day for at least ten days was well tolerated. In several clinical studies, consumption of xanthan gum in infant formula or formula for special medical purposes in infant was well tolerated up to concentration of 1,500 mg/L (232 mg/kg bw per day).

Potassium sorbate

Potassium sorbate is widely used as a chemical preservative and antibacterial in food, wines and personal-care products and due to its long history as a food additive with no apparent toxic effects, it recognized as GRAS [21 CFR 182.3640]. The maximal acceptable daily intake for human consumption was established to be 25 mg/kg [FAO, 2013]. The EFSA recently issued a scientific opinion re-evaluating sorbic acid (E 200), potassium sorbate (E 202) and calcium sorbate (E 203) when used as food additives [EFSA, 2019]. The Panel was requested by the European Commission to carry out a

scientific evaluation of an extended one-generation reproductive toxicity study (EOGRTS) to determine whether it would allow reconsideration of the temporary group acceptable daily intake (ADI) for sorbic acid (E 200) and potassium sorbate (E 202), established by the Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) in 2015. From the EOGTRS, the FAF Panel identified a lower confidence limit of the benchmark dose (BMDL) of 1,110 mg sorbic acid/kg body weight (bw) per day. By applying a default uncertainty factor of 100, the Panel established a group ADI expressed as 11 mg sorbic acid/kg bw per day for sorbic acid (E 200) and its potassium salt (E 202).

Table 3 -Summary of exposure to sorbic acid – sorbates (E 200, 202, 203) from its use as a food additive.

	Toddlers (12–35 months)	Children (3–9 years)	Adolescents (10–17 years)	Adults (18–64 years)	The elderly (≥ 65 years)
Regulatory maximum level exposure assessment scenario					
Mean	7.7–23.7	10.1–19.9	4.7–11.5	5.0–8.9	5.0–7.1
High level	20.7–33.9	20.0–38.7	10.1–25.1	9.9–16.3	9.6–12.8

Source: Table 3 in EFSA re-evaluation of sorbic acid (E 200), potassium sorbate (E 202) and calcium sorbate (E 203) as a food additive

In this assessment, mean exposure to sorbate ranged from 7.7 mg/kg bw per day in infants to 583 mg/kg bw per day in toddlers below the age of 3 years.

In this assessment, mean exposure to sorbate ranged from 7.7 mg/kg bw per day in infants to 583 mg/kg bw per day in toddlers below the age of 3 years.

Citric Acid and its tribasic salt

Citric acid is an intermediary substance in human metabolism, being engaged in the tricarboxylic acid cycle. Citric acid also occurs in many foods, with the highest levels found in citrus fruits. Orange juice and lemon juice contain citric acid at levels of approximately 10 and 50 g/L, respectively. JECFA established a group Acceptable Daily Intake (ADI) "not limited" for citric acid and its calcium, potassium and sodium salts (WHO 1974). The term ADI "not limited" is no longer used has the same meaning as the current term ADI "not specified", which is applicable to a food substance of very low toxicity for which the total dietary intake of the substance arising from its use at the levels necessary to achieve the desired effect and from its acceptable background levels in food, does not, in the opinion of JECFA, represent a hazard to health. Establishment of an ADI for citric acid expressed in numerical form was therefore not deemed necessary by JECFA.

They are used as an effective alkalinizing agent in several oral formulations (e.g Sodium Citrate and Citric Acid Oral Solution USP) for systemic alkalization (e.g in chronic metabolic acidosis) or as buffering agent (to neutralize gastric hydrochloric acid). Usual paediatric dosage can range between 300 – 1500 mg twice a day.

Estimated Intake of Excipients for Netupitant Paediatric Oral Suspension

For cross comparison reasons, the Applicant has evaluated the individual excipients intake in the NEPA-15-31 study for all the age groups; the mean body weight for each subgroup has been used as reference for this estimation. Data are presented in Table 4 below.

Overall the amounts of the excipients in the IMP formulations are all significantly well below the MDE levels established for approved human medicines described in Table 1.

Their dosage levels appear all to be much lower than those levels recommended in literature, guidances or based on food additives and flavouring regulations.

Table 4: Netuptiant paediatric oral suspension excipients estimated intake in paediatric patients (all ages) in study NEPA-15-31

Excipient	1-<3 months[3] (n = 1)			3-<6 months (n = 5)		6-<12 months (n = 9)		1-<2 years (n = 7)		2-<5 year (n = 12)		5-<12 year (n = 16)		12-<18 year (n = 12)	
	Corr. Factor	Mean bw (kg)	Total exp. (mg)	Mean bw (kg)	Total exp (mg)	Mean bw (kg)	Total exp (mg)	Mean bw (kg)	Total exp. (mg)	Mean (kg)	Total exp. (mg)	Mean (kg)	Total exp. (mg)	Mean (kg)	Total exp. (mg)
Glycerin 98%	0.61	4.71	**13.22**	5.66	26.04	8.06	37.08	9.72	44.71	14.61	67.21	25.70	118.22	57.72	**265.51**
Xanthan Gum	0.61	4.71	**0.80**	5.66	1.58	8.06	2.26	9.72	2.72	14.61	4.09	25.70	7.20	57.72	**16.16**
Potassium Sorbate	0.61	4.71	**0.26**	5.66	0.51	8.06	0.73	9.72	0.87	14.61	1.31	25.70	2.31	57.72	**5.19**
Citric Acid Anhydrous	0.61	4.71	**0.52**	5.66	1.02	8.06	1.45	9.72	1.75	14.61	2.63	25.70	4.63	57.72	**10.39**
Sodium Citrate Tribasic	0.61	4.71	**3.68**	5.66	7.24	8.06	10.32	9.72	12.44	14.61	18.70	25.70	32.90	57.72	**73.88**
Sorbitol Syrup n.c. 70%[1]	0.61	4.71	**168.65**	5.66	332.24	8.06	473.12	9.72	570.56	14.61	857.61	25.70	1508.5	57.72	**3388.16**
Purified Water	0.61	4.71	**60.25**	5.66	118.69	8.06	169.02	9.72	203.83	14.61	306.37	25.70	538.93	57.72	**1210.39**

n.c. denotes non-crystallizing ; n=total number of patients in the age groups for both treatment doses

Further considerations are presented below in respect of the different age groups in study NEPA-15-31 exposed to Netupitant Paediatric Oral Suspension.

Age groups for patients below 3 months of age (birth to <1 month and 1-<3 months)

As per study protocol, these two age groups had to be randomized to receive a reduced treatment dose, the netupitant doses were 0.8 mg/kg and 2.4 mg/kg in the two dose groups (instead of 1.33 mg/kg and 4 mg/kg), this based on ontogeny factors (e.g. CYP3A4 capacity, see study protocol). Conversely, the intake per Kg bw to excipients of the fixed dose paediatric formulation was reduced proportionally in this age groups by 40%. The excipients intake for these age groups is given in Table 5 below.

Table 5: Netuptiant paediatric oral suspension excipients intake in patients < 3 months

Age classes	bw (Min-Max[1])	Excipient	[redacted]	MDE (mg)	MDE per kg bw	ADI per kg bw	Max ADI per kg bw[2]
birth to <1 month	3.3 – 5.5	Glycerin 98%		31536	420 mg/kg	NA	3000 mg/kg
		Xanthan Gum		184	2.5 mg/kg	NA	214 mg/kg
		Potassium Sorbate		120 mg	1.6 mg/kg	11 mg/kg	25 mg/kg
1-<3 months	3.3 – 7.3	Citric Acid Anhydrous		510	6.8 mg/kg	NA	NA
		Sodium Citrate Tribasic		984	13.1 mg/kg	NA	NA
		Sorbitol		45000	600 mg/kg	NA[1]	20 g/day
		Purified Water		NA	NA	NA	NA

[1]Lower and higher 3rd centile of weight (www.cdc.gov/growthchart).
[2]The Max ADI is specified for adults. The Max ADI for glycerin of 3000 mg/kg is based on the lowest oral dose of glycerol required for therapeutic effect to be 125 mg/kg bw per hour
[1]140 mg/kg/day threshold.

Intake of potassium sorbate in these age groups is 1/200 the ADI, for xanthan gum and glycerin is less than 1/100 the Max ADI. For citric acid and its tribasic salt, amounts are less than 1/50 and 1/16 than the MDE. A paediatric patient with an average body weight of 5 kg would be therefore exposed to 35.81 mg/kg of sorbitol corresponding to a dose of 180 mg; this dose level represents 1/4 of threshold of 140 mg/kg/day.

Age groups for patients 3 months of age and older

As per study protocol, the patients belonging to age groups above 3 months of age (3 to <6 months, 6 to <12 months, 1 to <2 years, 2 to <5 years, 5 to <12 years, and 12 to <18 years) received the lower Netupitant 1.33 mg/kg dose (up to a maximum of 100 mg for patients weighing ≥75 kg) or the higher Netupitant 4 mg/kg dose (up to a maximum of 300 mg for patients weighing ≥75 kg). Patients weighing ≥75 kg will receive the entire 100 mg/7mL or 300 mg/7mL netupitant suspension, the quantitative amount of excipients represents their max dosage intake.

The excipients estimate intake for these age groups is given in Table 6 below.

Table 6: Netuptiant paediatric oral suspension excipients intake in patients > 3 months

Age classes	bw (Min-Max)[1]	Excipient	[redacted]	MDE (mg)	MDE per kg bw	ADI per kg	Max ADI per kg bw[2]
3 to <6 months	4.8 – 9.5	Glycerin 98%		31536	420 mg/kg	NA	3000 mg/kg
6 to <12 months	6.5 – 12.4	Xanthan Gum		184	2.5 mg/kg	NA	214 mg/kg
1 to <2 years	8.6 -15.1-	Potassium Sorbate		120 mg	1.6 mg/kg	11 mg/kg	25 mg/kg
2 to <5 years	10.6 -23.3	Citric Acid		510	6.8 mg/kg	NA	NA
5 to <12 years	15.1 – 59.0	Sodium Citrate		984	13.1 mg/kg	NA	NA
12 to <18 years	30.4 – 85.7	Sorbitol		45000	600 mg/kg	NA[1]	20 g/day
		Purified Water		NA	NA	NA	NA

[1]Lower and higher 3rd centile of weight (www.cdc.gov./growthchart). Weight base intake per kg bw up to patients weighing kg 75. Patients ≥75 kg receive the same fixed dose as 75kg patients.

Intake of sorbate in these age groups is less than 1/100 the ADI, for xantam gum it is less than 1/9 the MDE and 1/750 the recommended Max ADI. Glycerin amount remain very low, 1/650 the Max ADI. For citric acid and its tribasic salt, intakes are less than 1/35 and 1/10 than the respective MDE. A paediatric patient with an average weight of 10 kg would be therefore exposed to 58.7 mg/kg of sorbitol corresponding to a dose of 587 mg: This dose level represents less than 1/2 of threshold of 140 mg/kg/day and is deemed safe considering that common pharmaceutical medicines given orally in children contains 1-2 g of sorbitol per dose with highest sorbitol dose levels in the range 400–500 mg/kg.

The max intake to sorbitol is for patients with a weight of 75 kg or ≥75 kg who will be exposed to 58.7 mg/kg of sorbitol corresponding to a dose of approx 4405 mg.

Safety Review and Risk assessment for excipients

An evaluation of the excipients, their potential safety concerns and associated risk is presented in Table 7 below. Overall no risk has been identified in relation to the dose levels for Xanthan Gum, Citric Acid and its tribasic salt and Potassium Sorbate; their selection appear well justified considering the known safety concerns associated with excipients of the same function commonly used in paediatric populations as well as documented in literature.

The most relevant AEs related to sorbitol and glycerol are pertaining to the gastrointestinal system. Therefore, a search in the clinical data base was run to identify treatment emergent adverse events in the SOC Gastrointestinal Disorders.

In total, 19 events occurred in 13 patients (see Listing in Appendix 1). With particular regard to patients below the age of 3 years, 6 events were reported in 3 patients. The events of 'nausea' (1), 'vomiting' (4) and 'stomatitis' (1) were all considered not related to the study drugs netupitant and palonosetron.

Overall, no safety concerns were detected.

Table 7: Characteristics of excipients used in Netupitant Paediatric Oral Suspension and safety concerns and associated risk

Excipient	Function	Safety concern / Risk	Known safety concerns of other excipients with the same function used in common paediatric formulations
Glycerin 98%	Wetting agent	None, it is very well tolerated.	Not applicable
Xanthan Gum	Suspending agent	None, it is very well tolerated.	Not applicable
Potassium Sorbate	Preservative agent	None, it is very well tolerated. There are no data showing any risk by using recommended concentrations of 0.1% Comparing to other excipients, potassium sorbate shows the best risk-benefit-relationship.	• Benzalkonium chloride has been associated with bronchospasm in paediatric patients[1] • benzyl alcohol, known to determine metabolic acidosis, seizures and gasping[2] • Sodium benzoate may increase the risk of jaundice in newborn babies. • Methyl hydroxybenzoate may cause allergic reactions • Propyl-hydroxybenzoate (PHB) may cause allergic reactions. PHB binds to oestrogen receptors but with a much weaker affinity than the natural ligand • Propylene glycol may cause alcohol-like symptoms
Citric Acid Anhydrous and Sodium Citrate Tribasic	pH modifier	None, they are both very well tolerated	Not applicable
Sorbitol Syrup n.c. 70%[1]	Sweetening / preservative agent	May cause problems in people with congenital fructose intolerance (c. 1:20,000 live births); osmotic laxative effect at a level higher than 140 mg/kg (equivalent of 10 g/70 kg). Risk for gastrointestinal symptoms is low at the level of 58.7 mg / kg for children 3 months of age and older or 35.8 mg /kg for those below 3 months of age.	• Lactose may cause gastrointestinal symptoms in intolerant subjects[5] • Sucrose is potentially cariogenic[6] • Aspartame as a source of phenylalanine may be harmful in subjects affected by phenylchetonuria[7] and has been associated with headache and seizures[8] • Saccharin could increase the risk of developing cancer or dermatological reactions[9]
Purified Water	Solvent	None	• Ethanol as CNS) depressant on neurones can lead to intoxication: in children, signs of ethanol intoxication are hypoglycaemia, hypothermia and coma.[10] • Propylene glycol at high doses have been associated with respiratory, cardiovascular, central and hepatic adverse effects in newborns[3,4]

[1]Miszkiel KA, Beasley R, Rafferty P, Holgate ST. The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. Br J Clin Pharmacol. 1988;25(2):157-63. [2]LeBel M, Ferron L, Masson M, Pichette J, Carrier C. Benzyl alcohol metabolism and elimination in neonates. Dev Pharmacol Ther. 1988;11(6):347-5. [3]Propylene glycol. Hazardous Substances Databank (HSDB) last update: May 2004. [4] Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. J Pediatr. 1978;93(3):515-6. [5] Duro D, Rising R, Cedillo M, Lifschitz F. Association between infantile colic and carbohydrate malabsorption from fruit juices in infancy. Pediatrics. 2002;109(5):797-805. [6]Aires CP, Tabchoury CP, Del Bel Cury AA, Koo H, Cury JA. Effect of sucrose concentration on dental biofi formed in situ and on enamel demineralization. Caries Res. 2006;40(1):28-32. [7]Stegink LD, Filer LJ, Bell EF, Ziegler EE, Tephly TR, Krause WL. Repeated ingestion of aspartame-sweetened beverages: further observations in individuals heterozygous for phenylketonuria. Metabolism. 1990;39(10):1076-81. [8]Tollefson L, Barnard RJ. An analysis of FDA passive surveillance reports of seizures associated with consumption of aspartame. J Am Diet Assoc. 1992;92(5):598-601. [9]Walker AM, Dreyer NA, Friedlander E, Loughlin J, Rothman KJ, Kohn HI. An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. Am J Public Health. 1982;72(4):376-

Overall assessment and conclusion

The Applicant has evaluated the intake levels and the safety for all the excipients used in Netupitant Paediatric Oral Suspension for all age groups including their potential safety concerns and associated risk and those TAE of interest (SOC Gastrointestinal Disorders) in the paediatric patients below 3 years of age. No concerns arise from these assessments nor from the search in literature or guidances on their adequate use in paediatric oral formulations.

It should be noted that in comparison to other paediatric medicines, the dosage regimen for Netupitant Paediatric Oral Suspension is based on a single administration before each chemotherapy cycle to prevent CINV. The suspension is not intended for BID or TID regimen, or multiple days

administration such other medicines of the same class (ondansetron, emend) or commonly used in paediatry (antivirals, allergic rhinitis, epilepsy). Therefore, no risk can be associated to a multiple day administration as these medicines given daily, weekly or even longer period which would necessarily expose patients to excipients higher doses and their potential adverse effects. Even when the amount of the excipients is the same of another formulation for the same route this does not imply the level of risk would be the same. For sorbitol which is considered a potentially harmful excipient in the youngest children if it is given at high doses, data from databases related to approved drug products (dailymed, eMC, EMA) indicate that it is safely use being administered in all paediatric age groups (including neonates). From this search emerges over 70 products containing sorbitol at different dose levels, and a large number of medicines is approved for paediatric use.

A comparison of the dose levels in Netupitant Paediatric Oral Suspension versus well established oral paediatric approved products is given in Table 8 and Table 9.

Based on this comparison, we believe the dose level of sorbitol (as well as all the other excipients) in Netupitant Paediatric Oral Suspension single dose regimen can be safe for the overall paediatric population with no Hereditary Fructose Intolerance (HFI).

Table 8 Comparison of Sorbitol estimated intake in Netupitant suspension versus common approved paediatric medicines (≤ 40kg)

	Netupitant Paediatric Oral Suspension (100 mg/7 ml)	**Tamiflu 6 mg/ml powder for oral suspension[3]** children including full term neonates (Treatment of influenza) or 1 year of age or older (Prevention of influenza)						**Ondansetron 4mg/5ml Oral Solution[4]** children aged ≥6 months (CINV management)		
	Given once only before chemo Cycle	Recommended dose for 5 days (or 10 days for Immunocompromised Patients)		Sorbitol intake (mg)				Weight-based dosing for Chemotherapy	Sorbitol intake (mg)	
Body Weight	Sorbitol intake (58.7 mg / kg)[1]	Oseltamivir 6 mg/ml	Amount of oral suspension to withdraw	Intake per oral suspension dose*	Daily intake	Five days intake	Ten days intake	Ondansetron syrup on Days 2-6	Daily intake	Five days intake (Days 2-6)
3		9 mg twice daily	1.5 ml twice daily	**270**	**540**	**2700**	**5400**	2 mg every 12 hours		
3.3 kg	**118**	(9.9 twice daily)	(1.67 ml twice daily)	**301**	**601**	**3006**	**6012**	2 mg every 12 hours		
4 kg	**143**	12 mg twice daily	2.0 ml twice daily	**360**	**720**	**3600**	**7200**	2 mg every 12 hours		
5 kg	**179 (294)[2]**	15 mg twice daily	2.5 ml twice daily	**450**	**900**	**4500**	**9000**	2 mg every 12 hours		
6 kg	**215 (352)[2]**	18 mg twice daily	3.0 ml twice daily	**540**	**1080**	**5400**	**10800**	2 mg every 12 hours	**1960**	**9800**
7 kg	**250 (411)[2]**	21 mg twice daily	3.5 ml twice daily	**630**	**1260**	**6300**	**12600**	2 mg every 12 hours	**1960**	**9800**
8 kg	**470**	24 mg twice daily	4.0 ml twice daily	**720**	**1440**	**7200**	**14400**	2 mg every 12 hours	**1960**	**9800**
9 kg	**528**	27 mg twice daily	4.5 ml twice daily	**810**	**1620**	**8100**	**16200**	2 mg every 12 hours	**1960**	**9800**
10 kg	**587**	30 mg twice daily	5.0 ml twice daily	**900**	**1800**	**9000**	**18000**	2 mg every 12 hours	**1960**	**9800**
15 kg	**881**	45 mg twice daily	7.5 ml twice daily	**1300**	**2600**	**13000**	**26000**	4 mg every 12 hour	**3920**	**19600**
20 kg	**1174**	45 mg twice daily	7.5 ml twice daily	**1300**	**2600**	**13000**	**26000**	4 mg every 12 hour	**3920**	**19600**
25 kg	**1468**	60 mg twice daily	10 ml twice daily	**1700**	**3400**	**17000**	**34000**	4 mg every 12 hour	**3920**	**19600**
30 kg	**1761**	60 mg twice daily	10 ml twice daily	**1700**	**3400**	**17000**	**34000**	4 mg every 12 hour	**3920**	**19600**
35 kg	**2055**	60 mg twice daily	10 ml twice daily	**1700**	**3400**	**17000**	**34000**	4 mg every 12 hour	**3920**	**19600**
40 kg	**2348**	60 mg twice daily	10 ml twice daily	**1700**	**3400**	**17000**	**34000**	4 mg every 12 hour	**3920**	**19600**
> 40 kg		75 mg twice daily	12.5 ml twice daily	**2100**	**4200**	**2100**	**42000**			

[1] For patients less than 3 months of age sorbitol intake is 35.8 mg/kg (up to 7.3 kg of weight for 3 months of age: higher 3rd centile of weight)

[2] Patients from 3-<6 months and older (min weight 4.8 kg: lower 3rd centile of weight) sorbitol intake is 58.7 mg / kg (corresponding to 294 mg for a 5 kg patients).

[3] 5 ml oseltamivir suspension delivers 0.9 g of sorbitol and 2.5 mg of sodium benzoate; 7.5 ml oseltamivir suspension delivers 1.3 g of sorbitol and 3.75 mg of sodium benzoate 10 ml oseltamivir suspension delivers 1.7 g of sorbitol and 5.0 mg of sodium benzoate; 12.5 ml oseltamivir suspension delivers 2.1 g of sorbitol and 6.25 mg of sodium benzoate. The recommended treatment dose for infants 0 - 12 months of age is 3 mg/kg twice daily. For Children 1 to 12 years of age, weight-adjusted dosing regimens, BW 10 kg to 15 kg dose is 30 mg twice daily, > 15 kg to 23 kg dose is 45 mg twice daily, > 23 kg to 40 kg dose is 60 mg twice daily, > 40 kg dose is 75 mg twice daily. Adults, and adolescents 13 years and over with BW > 40 kg treatment dose is 75 mg twice daily. Children weighing > 40 kg and who are able to swallow capsules may receive prophylaxis with a 75 mg capsule once daily for 10 days as an alternative to the recommended dose of Tamiflu suspension.

[4] Each 5 ml also contains 1960 mg of sorbitol, 10 mg sodium benzoate, 11.45 mg sodium and 11.375 mg propylene glycol. Intake is calculated for patients 6 month of age and older (over 6 kg of weight). The Day 1 dose of ondansetron is given IV: as a single intravenous dose of 0.15mg/kg, the dose must not exceed 8mg.

Table 9 Comparison of Sorbitol estimated intake in Netupitant suspension versus oral approved paediatric medicines (≤ 40 kg)

	Netupitant Paediatric Oral Suspension (100 mg/7 ml)	Neoclarityn 0.5 mg/ml oral solution[3] (adolescents and children over 1 year of age)			Vimpat 10 mg/ml syrup[4] (adolescents and children from 4 years of age)[5]					
	Given once only (before each chemotherapy Cycle)	Ml of solution (desloratadine dose mg)	Sorbitol intake (150 mg/ml)		Daily intake				Sorbitol Weekly intake (mg)	
Body Weight	Sorbitol intake (58.7 mg / kg[1])	2.5 ml (1.25 mg)	Daily intake	Weekly intake	Lacosamide 0.1 ml/kg (1 mg/kg) Starting dose	Sorbitol intake (187 mg ml)	Lacosamide 0.6 ml/kg (6 mg/kg) Max. rec.dose	Sorbitol intake (187 mg ml)	Sorbitol Min (lacosamide Starting dose)	Sorbitol Max (lacosamide Max rec dose)
3.3 kg	**118**									
5 kg	**179 (294)**[2]									
8 kg	**470**	2.5 ml	**375**	**2625**						
9 kg	**528**	2.5 ml	**375**	**2625**						
10 kg	**587**	2.5 ml	**375**	**2625**						
15 kg	**881**	2.5 ml	**375**	**2625**	1.5 ml (15 mg)	**280**	9 ml (90 mg)	**1683**	**1963**	**11781**
20 kg	**1174**	2.5 ml (1 -5 years) 5 ml (6 -11 years)	**375**	**2625**	2 ml (20 mg)	**374**	12 ml (120 mg)	**2244**	**2618**	**15708**
25 kg	**1468**	5 ml	**750**	**5250**	2.5 ml (25 mg)	**467**	15 ml (150 mg)	**2805**	**3272**	**19635**
30 kg	**1761**	5 ml	**750**	**5250**	3 ml (30 mg)	**561**	18 ml (180 mg)	**3366**	**3927**	**23562**
35 kg	**2055**	5 ml (6 -11 years) 10 ml (12 -17 years)	**750** **1500**	**5250** **10500**	3.5 ml (35 mg)	**654**	21 ml (210 mg)	**3927**	**4581**	**27489**
40 kg	**2348**	5 ml (6 -11 years) 10 ml (12 -17 years)	**750** **1500**	**5250** **10500**	4 ml (40 mg)	**748**	20 ml (200 mg)[4]	**3740**	**5236**	**26180**

[1] For patients less than 3 months of age sorbitol intake is 35.8 mg/kg (up to 7.3 kg of weight for 3 months of age: higher 3rd centile of weight).
[2] Patients from 3-<6 months and older (min weight 4.8 kg: lower 3rd centile of weight) sorbitol intake is 58.7 mg / kg (corresponding to 294 mg for a 5 kg patients).
[3] Neoclarityn 0.5 mg/ml oral solution SPC "Each ml of oral solution contains 0.5 mg desloratadine, it contains 150 mg/ml of sorbitol. Indication: adolescents and children over the age of 1 year for the relief of symptoms associated with: allergic rhinitis, urticarial. Children 1 through 5 years of age: 2.5 ml (1.25 mg) Neoclarityn oral solution once a day. Children 6 through 11 years of age: 5 ml (2.5 mg) Neoclarityn oral solution once a day. Adults and adolescents (12 years of age and over) - the recommended dose of Neoclarityn is 10 ml (5 mg) oral solution once a day."
[4] In children weighing less than 40 kg, a maximum dose of up to 12 mg/kg/day is recommended. In children weighing from 40 to under 50 kg, a maximum dose of 10 mg/kg/day is recommended. For Adolescents and children weighing 50 kg or more, the starting dose is 100 mg/day or 200 mg/day, the Maximum recommended dose is up to 600 mg/day. Children and adolescents less than 50 kg should preferably start the treatment with Vimpat 10 mg/ml syrup. Vimpat 10 mg/ml solution for infusion is an alternative for patients when oral administration is temporarily not feasible. It is therefore recommended to initiate treatment with the syrup and switch to tablets, if desired. [5] Lacosamide is under paediatric development for Treatment of epilepsy with partial onset seizures in patients from birth to less than 18 years of age (EMEA-000402-PIP02-11-M05).

Assessment of the response

While the comparison of the composition of netupitant versus other medicines licensed in Europe for use in the paediatric population is noted and understood, it is important to remember that many medicines for use in this population were licensed prior to the introduction of the Paediatric Regulation 1901 of 2006, and as such there may not have been the same appreciation of the specific requirements for appropriate evidence supporting the licensing of age-appropriate formulations for the various age cohorts, nor the characterisation of the safety profile of the excipients used in those various products. As such, existing medicines for a specific age cohort containing a specific excipient is not in itselfinsufficient justification, and therefore can only be considered as supportive.

The applicant has detailed the function and amount of each excipient used in the netupitant formulation, and also has calculated the amount per Kg bodyweight which would be expected to be administered to children of typical bodyweight for the various paediatric age cohorts in which the product is intended to be used. They have also compared this amount to the amounts considered to be safe, as published in the various compendia, pharmacopoeias, and guidance documents which contain information related to the known or presumed safe Maximum Daily Exposure (MDE) level. For some of these, the only reference texts available relate to the amounts of the various excipients which are considered safe for use in foods, and while this is not ideal it can be accepted that this is the currently best available evidence supporting these reference values. As such, these can be accepted. It can be seen from the applicant's calculations that the amounts anticipated to be administered fall comfortably within these reference ranges. In addition, as the product is likely to be used as a single dose on different occasions generally separated in time, any risk of accumulation is likely to be low. While it might have been ideal for the applicant to clarify the known pharmacokinetics of the various excipients with a view to describing how these might differ in the various paediatric age cohorts, it is accepted on this occasion that the amounts being used and the dosing intervals allowed are such as to minimise any concerns from a clinical perspective. Justification of the safety of the proposed excipient levels based on the basis of available/calculated permitted daily exposures (PDEs) would be more preferable from a risk assessment perspective. Maximum daily exposure limits in other products will have been based on a benefit/risk assessment for that particular drug product and the patient population and indication. Nevertheless, based on the additional information and assessment provided by the MAH the proposed levels appeared justified.

Applicants should remain mindful of the advice contained within the guidance on the development of medicines for use in the paediatric population, which advises that a proper justification for the choice and amounts of all excipients used in a paediatric formulation should be presented, and that only those excipients which are essential to ensure the proper functioning and acceptability of the product should be included in the formulation. In general, a full characterisation of the safety aspects of those excipients in all relevant paediatric populations should be provided, taking into account the anticipated developmental and metabolic differences which exist at the various age cohorts, especially neonates and infants. It is also important for applicants to indicate any areas where information on this is either unavailable or uncertain. This allows a full assessment of the benefits and potential risks of the use of that formulation in the various paediatric age cohorts to be made. Applicants are reminded of the requirements set out in the Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2), as well as the other relevant QWP guidelines.

Overall, despite the deficiencies in the response, the conclusions of the assessor is that the nature of the product and the levels of the excipients are such as to conclude that the benefit/risk profile of this product for this particular condition is positive.

Overall conclusion

Issue Resolved

Question 2

The clarification by the applicant regarding the reason for the apparent differences between the PK profiles of the lower netupitant dose in younger children versus other groups is plausible and can be accepted. However, while it is accepted that inter-patient variability might have played a part in the apparently increased exposure of the two patients to the medicine, the levels of both Cmax and AUC seem significantly high as to wonder whether any dosing errors occurred in these patients.

The applicant is asked to confirm that the patients did indeed receive the correct dose, and if so comment on the reasons why the observed values were so beyond what might have been expected given the known degree of variability of netupitant.

Summary of Applicant's Response

According to the information reported in the eCRFs of patients #101168 and #301141 of the 6 months to < 12 months age class, dosing errors could be excluded.

Reasons that may explain higher netupitant exposure (C_{max} and AUC_{0-inf}) in these patients may refer to the known inter-patient variability of netupitant pharmacokinetics and, possibly, to potential drug interactions with concomitant therapies.

The eCRFs indicate that before receiving the oral NEPA treatment, patients #101168 and #301141 were exposed to drugs characterized by strong CYP3A4 inhibition properties such as the antimycotic drugs fluconazole (#101168 only) and posaconazole (both #101168 and #301141). Treatment with fluconazole and posaconazole was terminated 11 days before NEPA administration, according to the study protocol. However, a possible residual drug interaction with fluconazole and posaconazole cannot be excluded. This might have contributed to explain higher netupitant exposure for patients #101168 and #301141, this latter in particular. The other two patients in the same age class, i.e., #302125 and #404150, who did not show increased netupitant C_{max} and AUC_{0-inf}, did not receive any concomitant medications that may have affected netupitant exposure.

Exposure data for netupitant metabolites M1, M2 and M3 appear to support this hypothesis. The table below shows that the AUC_{0-inf} and C_{max} metabolite-to-netupitant ratios for patients #101168 and #301141 are remarkably lower than those estimated for the other two patients of the 6 months to < 12 months age class, suggesting a reduced metabolism in these patients that may explain the higher exposure to the parent drug.

Age Class	SUBJID	Dose	Gender	AUC_{0-inf} ratio			C_{max} ratio		
		(mg/kg)		M1/Netu	M2/Netu	M3/Netu	M1/Netu	M2/Netu	M3/Netu
6 mo to < 12 mo	101168	1.33	F	0.27	0.35	0.23	0.09	0.27	0.13
6 mo to < 12 mo	301141	1.33	F	0.12	0.18	0.06	0.07	0.28	0.08
6 mo to < 12 mo	302125	1.33	F	0.50	0.55	0.46	0.19	0.59	0.15
6 mo to < 12 mo	404150	1.33	M	1.95	1.79	0.90	0.18	1.49	0.12

Assessment of the response

The applicant has provided pharmacokinetic data for both patients showing a reduction in the metabolism of the parent compound into its metabolites, and suggests that this may be as a result of concomitant exposure to the strong CYP3A4 inhibitors fluconazole and posaconazole.

While this is a possibility, it is noted by the assessor that the elimination half-lives of both substances is approximately 30h, which would mean that more than 8 half-lives would have elapsed if patients had indeed stopped taking these medicines prior to NEPA administration. As such, it might be expected that any residual inhibition of these medicines would have sufficiently waned so as not to have had an effect on the metabolism of NEPA.

That being said, the assessor is satisfied that no overt errors occurred regarding the doses administered in the trial and that these specific results did not impact the overall results on the trial.

Overall conclusion

Issue resolved

2.3.3. Discussion on clinical aspects

N/a

3. CHMP overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.